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*Reacción de cicloadición 1,3-dipolar azida-alqueno
intramolecular: Aplicaciones en síntesis de heterociclos
y productos naturales.*



TESIS DOCTORAL

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A mis padres

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Abreviaturas empleadas

AcO	acetoxi
Ar	aromático
DBU	1,8-diazabicyclo[5.4.0]undec-7-eno
Boc	<i>tert</i> -butoxicarbonil
<i>n</i> -BuLi	<i>n</i> -butil litio
<i>t</i> -BuOK	<i>tert</i> -butóxido potásico
CAN	nitrato cérico amónico
CCF	cromatografía en capa fina
DCM	diclorometano
DIAD	azodicarboxilato de dietilo
DIBAL	hidruro de diisobutil aluminio
DMAP	4-dimetilaminopiridina
DMF	<i>N,N'</i> -dimetilformamida
EDCI	1-(3-dimetilaminopropil)-3-etilcarbodiimida
ESI	ionización por electrospray
EtOH	etanol
EWG	grupo electroatrayente
FTIR	espectroscopía de Infrarrojo por Transformada de Fourier
HMPA	hexametilfosforamida
HRMS	espectroscopía de masas de alta resolución
KHMDS	hexametildisilazida de potasio
LDA	diisopropilamida de litio
MeOH	metanol
Ms	metanosulfonilo
MW	microondas
NMO	óxido de metilmorfolina
Nu	nucleófilo

PCC	clorocromato de piridinio
PPTS	<i>p</i> -toluensulfonato de piridinio
RMN/NMR	resonancia magnética nuclear
t.a.	temperatura ambiente
TBAF	fluoruro de tetrabutilamonio
TBDPS	<i>tert</i> -butildifenilsililo
TBS	tributilsilano
TFA	ácido trifluoroacético
TFE	trifluoroetanol
THF	tetrahidrofurano
TMS	tetrametilsilano
TPAP	perrutenato de tetrapropilamonio
Ts	<i>p</i> -toluensulfonilo
p-TsOH	ácido <i>p</i> -toluensulfónico
UV	ultravioleta

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Capítulo 1

INTRODUCCIÓN Y OBJETIVOS

1.1.-INTRODUCCIÓN.

1.1.1.- Iminas cíclicas: síntesis y aplicaciones.

Los heterociclos nitrogenados en general y las iminas cíclicas en particular, son un motivo estructural muy abundante en química orgánica que se encuentra presente en muchos productos naturales con interesantes propiedades biológicas y farmacéuticas.¹ Centrándonos en las iminas cíclicas encontramos por ejemplo la familia de las gimnodiminas,² un grupo de toxinas marinas que poseen en su estructura una imina espirocíclica la cual es la responsable de su actividad mediante la unión a los receptores nicotínicos de acetilcolina (Figura 1.1).³ Igualmente las lanopilinas son otro grupo de compuestos con una imina cíclica en su estructura que fueron aislados de una cepa de *Streptomyces* y que son capaces de inhibir la enzima lanosterol sintasa, por lo que podrían ser empleados en el tratamiento de la hipercolesterolemia.⁴

Por otro lado, especialmente las iminas cíclicas de cinco y seis miembros (1-pirrolinas y 1-piperideinas respectivamente) son importantes intermedios para la síntesis de otras estructuras como sus análogos saturados, las pirrolinas y piperidinas;⁵ o sistemas bicíclicos como los anillos de pirrolizidina, indolizidina y quinolizidina,⁶ estructuras también muy comunes en la naturaleza.⁷ Su gran importancia en química orgánica queda patente igualmente en la síntesis total de alcaloides, ya que son muchos los ejemplos de síntesis totales en los que se emplea una imina cíclica como intermedio clave.⁸

¹ a) A. Cembella, B. Krock, en *Cyclic Imine Toxins: Chemistry, Biogeography, Biosynthesis and Pharmacology en Seafood and Freshwater Toxins: Pharmacology, Physiology and Detection*, Ed. Luis M. Botana, CRC Press, **2008**; b) A. Otero, M.-J. Chapela, M. Atanassova, J. M. Vieites, A. G. Cabado, *Chem. Res. Toxicol.* **2011**, *24*, 1817-1829.

² a) T. Seki, M. Satake, L. Mackenzie, H. Kaspar, T. Yasumoto, *Tetrahedron Lett.* **1995**, *36*, 7093-7096; b) M. Stewart, J. W. Blunt, M. H. G. Munro, W. T. Robinson, D. J. Hannah, *Tetrahedron Lett.* **1997**, *38*, 4889-4890; c) C. O. Miles, A. L. Wilkins, D. J. Stirling, A. L. MacKenzie, *J. Agric. Food Chem.* **2000**, *48*, 1373-1376; d) C. O. Miles, A. L. Wilkins, D. J. Stirling, A. L. MacKenzie, *J. Agric. Food Chem.* **2003**, *51*, 4838-4840.

³ a) Y. Bourne, Z. Radic, R. Araújo, T. T. Talley, E. Benoit, D. Servent, P. Taylor, J. Molgó, P. Marchot, *Proc. Natl. Acad. Sci.* **2010**, *107*, 6076-6081; b) R. Araújo, D. Servent, J. Molgó, B. I. Iorga, C. Fruchart-Gaillard, E. Benoit, Z. Gu, C. Stivala, A. Zakarian, *J. Am. Chem. Soc.* **2011**, *133*, 10499-10511.

⁴ Y. Sakano, M. Shibuya, A. Matsumoto, Y. Takahashi, H. Tomoda, S. Oh Mura, Y. Ebizuka, *J. Antibiot.* **2003**, *56*, 817-826.

⁵ a) M. Chang, W. Li, G. Hou, X. Zhang, *Adv. Synth. Catal.* **2010**, *352*, 3121-3125; b) N. E. Shevchenko, E. S. Balenkova, G.-V. Rösenthaller, V. G. Nenajdenko, *Synthesis*, **2010**, 120-126; c) S. Guo, Y. Xie, X. Hu, H. Huang, *Org. Lett.* **2011**, *13*, 5596-5599.

⁶ Para algunos ejemplos de síntesis de pirrolizidinas, indolizidinas o quinolizidinas a partir de iminas cíclicas ver: a) K. A. Tehrani, M. D'hooge, N. De Kimpe, *Tetrahedron*, **2003**, *59*, 3099-3108; b) V. V. R. Kondakal, M. I. Qamar, K. Hemming, *Tetrahedron Lett.* **2012**, *53*, 4100-4103; c) Y. Mirabal-Gallardo, M. D. P. C. Soriano, J. Caballero, J. Alzate-Morales, M. J. Simirgiotis, L. S. Santos, *Synthesis*, **2012**, *44*, 144-150.

⁷ Para una revisión sobre alcaloides de pirrolizidina ver: J. R. Liddell, *Nat. Prod. Synth.* **2002**, *19*, 773-781; Para una revisión sobre alcaloides de indolizidina y quinolizidina ver: J. P. Michael, *Nat. Prod. Rep.* **2007**, *24*, 191-222.

⁸ Para una revisión sobre el empleo de iminas y entre ellas iminas cíclicas en síntesis total de productos naturales ver: S. F. Martin, *Pure Appl. Chem.* **2009**, *81*, 195-204. Algunos ejemplos de síntesis totales de productos naturales en los que se aparece una imina cíclica como intermedio: a) A. Lerchner, E. M. Carreira, *J. Am. Chem. Soc.* **2002**, *124*, 14826-14827; b) T. Itoh, M. Miyazaki, H. Fukuoaka, K. Nagata, A. Ohsawa, *Org. Lett.* **2006**, *8*, 1295-1297; c) A. Chandra, J. A. Pigza, J.-S. Han, D. Mutnick, J. N. Johnston, *J. Am. Chem. Soc.* **2009**, *131*, 3470-3471.

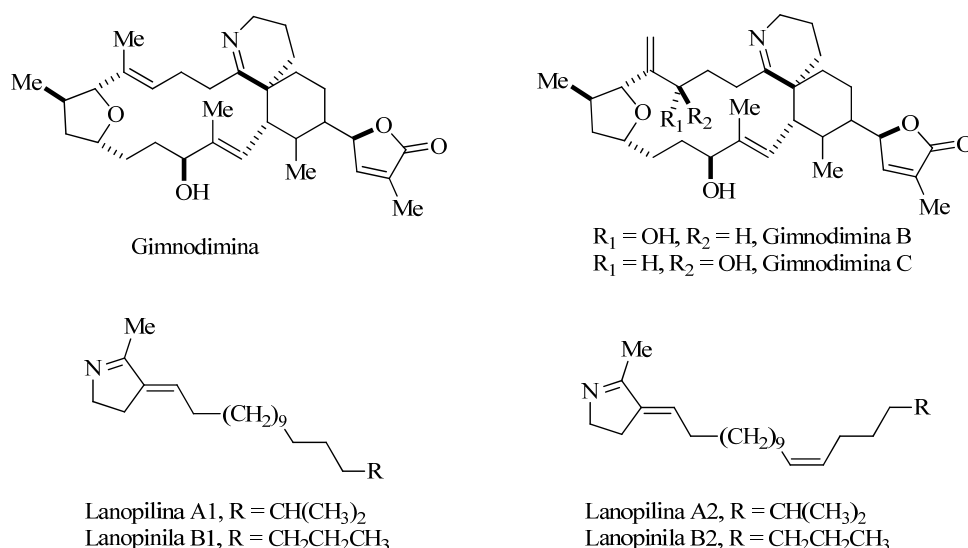


Figura 1.1. Productos naturales con una imina en su estructura.

Dadas todas estas propiedades y aplicaciones de las iminas cíclicas, en los últimos años se han desarrollado muchas estrategias para su síntesis. Seguidamente se citarán los métodos más importantes, siendo cada uno de ellos ilustrado con un ejemplo en el Esquema 1.1. Así pues se pueden destacar la hidroaminación intramolecular de aminoalquinos⁹ y la aminación oxidativa de aminoalquenos,^{10,9b} reacciones de transposición de ciclopropiliminas¹¹ e hidrogenación parcial de pirroles¹² para la preparación de 1-pirrolinas, ciclación de ω-amino cetonas,¹³ adición de organometálicos a lactamas,¹⁴ adición de organometálicos a nitrilos,¹⁵ reacciones radicalicas¹⁶ o diferentes reacciones de cicloadición.¹⁷

⁹ a) Y. Fukuda, S. Matsubara, K. Utimoto, *J. Org. Chem.* **1991**, 56, 5812-5816; b) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, 98, 675-703; c) J. M. Carney, P. J. Donoghue, W. M. Wuest, O. Wiest, P. Helquist, *Org. Lett.* **2008**, 10, 3903-3906; d) V. B. R. Iska, V. Verdolino, O. Wiest, P. Helquist, *J. Org. Chem.* **2010**, 75, 1325-1328.

¹⁰ a) T. Kondo, T. Okada, T. Mitsudo, *J. Am. Chem. Soc.* **2002**, 124, 186-187; b) C. S. Yi, S. Y. Yun, *Organometallics*, **2004**, 23, 5392-5395.

¹¹ a) P. Caramella, R. Huisgen, B. Schmolke, *J. Am. Chem. Soc.* **1974**, 96, 2997-3000; b) P. J. Campos, A. Soldevilla, D. Sampedro, M. A. Rodriguez, *Org. Lett.* **2001**, 3, 4087-4089; c) P. J. Campos, A. Soldevilla, D. Sampedro, M. A. Rodriguez, *Tetrahedron Lett.* **2002**, 43, 8811-8813; d) A. Soldevilla, D. Sampedro, P. J. Campos, M. A. Rodriguez, *J. Org. Chem.* **2005**, 70, 6976-6979.

¹² D.-S. Wang, Z.-S. Ye, Q.-A. Chen, Y.-G. Zhou, C.-B. Yu, H.-J. Fan, Y. Duan, *J. Am. Chem. Soc.* **2011**, 133, 8866-8869.

¹³ a) K. Pal, M. L. Behnke, L. Tong, *Tetrahedron Lett.* **1993**, 34, 6205-6208; b) P. N. D. Singh, R. F. Klima, S. Muthukrishnan, R. S. Murthy, J. Sankaranarayanan, H. H. Stahlecker, B. Patel, A. D. Gudmundsdóttir, *Tetrahedron Lett.* **2005**, 46, 4213-4217.

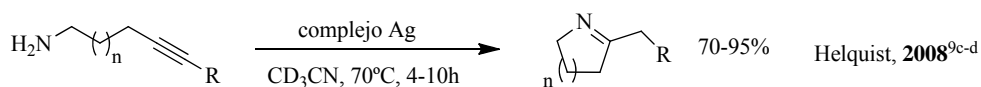
¹⁴ a) D. H. Hua, S. W. Miao, S. N. Bharathi, T. Katsuhira, A. A. Bravo, *J. Org. Chem.* **1990**, 55, 3682-3684; b) Y. Ahn, G. I. Cardenas, J. Yang, D. Romo, *Org. Lett.* **2001**, 3, 751-754.

¹⁵ a) D. F. Fry, C. B. Fowler, R. K. Dieter, *Synlett*, **1994**, 10, 836-838; b) D. F. Fry, M. Brown, J. C. McDonald, *Tetrahedron Lett.* **1996**, 37, 6227-6230; c) S. Sanjaya, S. Chiba, *Tetrahedron*, **2011**, 67, 590-596.

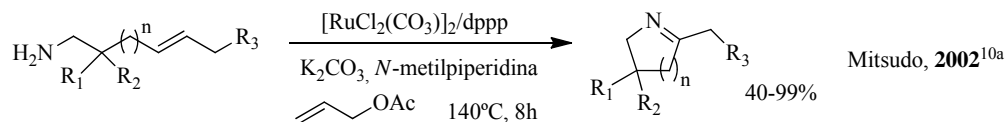
¹⁶ a) J. Boivin, E. Fouquet, S. Z. Zard, *Tetrahedron Lett.* **1990**, 31, 85-88; b) P. Srivastava, L. Engman, *Tetrahedron Lett.* **2010**, 51, 1149-1151.

¹⁷ a) T. Saegusa, Y. Ito, H. Kinoshita, S. Tomita, *J. Org. Chem.* **1971**, 36, 3316-3323; b) W. H. Pearson, E. P. Stevens, *J. Org. Chem.* **1998**, 63, 9812-9827; c) G. Sathishkannan, K. Srinivasan, *Org. Lett.* **2001**, 13, 6002-6005; d) S. Peddibhotla, J. J. Tepe, *J. Am. Chem. Soc.* **2004**, 126, 12776-12777; e) A. D. Melhado, M. Luparia, F. D. Toste, *J. Am. Chem. Soc.* **2007**, 129, 12638-12639; f) M. P. Sibi, T. Soeta, C. P. Jasperse, *Org. Lett.* **2009**, 11, 5366-5369.

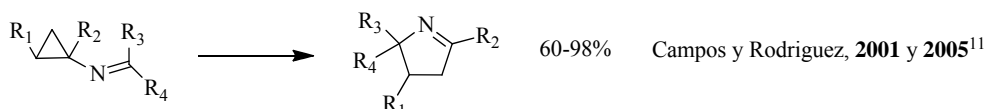
Hidroaminación intramolecular de aminoalquinos



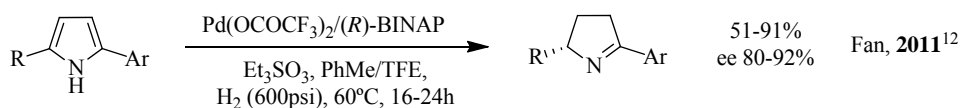
Aminación oxidativa de aminoalquenos



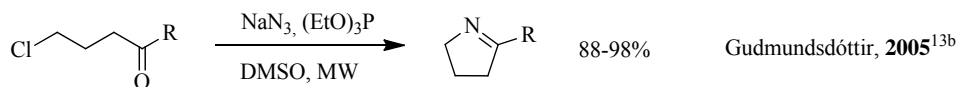
Transposición de ciclopropiliminas



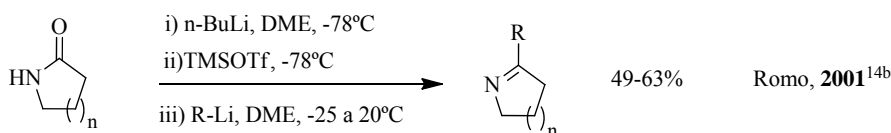
Hidrogenación parcial de pirroles



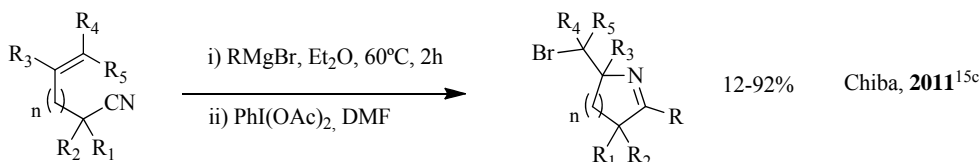
Ciclación de amino cetonas



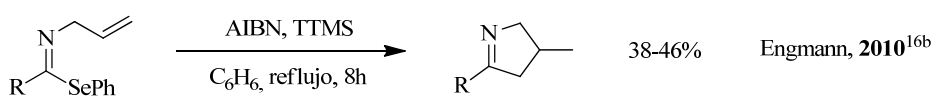
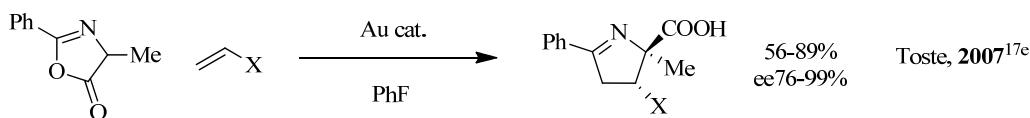
Adición de organometálicos a lactamas



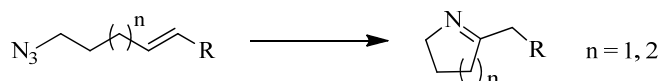
Adición de organometálicos a nitrilos



Esquema 1.1. Metodologías para la síntesis de iminas cíclicas.

Reacciones radicalicas**Reacciones de cicloadición****Esquema 1.1.** Metodologías para la síntesis de iminas cíclicas.

Es precisamente en el ámbito de las reacciones de cicloadición donde se encuadra esta tesis doctoral en la que se emplea la reacción de cicloadición 1,3-dipolar azida-alqueno en su versión intramolecular para la síntesis de 1-pirrolinas y 1-piperideinas (Esquema 1.2). A continuación se presentarán los aspectos más importantes de las reacciones de cicloadición 1,3-dipolares y en concreto de la cicloadición azida-alqueno.

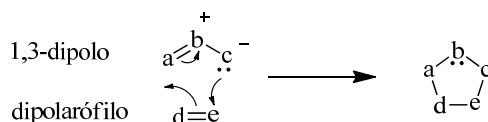
**Esquema 1.2.** Reacción de cicloadición 1,3-dipolar azida-alqueno intramolecular.**1.1.2.- Reacción de cicloadición 1,3-dipolar azida-alqueno.**

Las reacciones de cicloadición 1,3-dipolares son uno de los métodos más empleados para la construcción de sistemas heterocíclicos.¹⁸ En ellas un 1,3-dipolo reacciona con un dipolarófilo para formar un anillo de cinco miembros (Esquema 1.3).¹⁹ Así, un 1,3-dipolo se define como una especie que puede ser representada mediante una estructura octete zwitteriónica y que da lugar a cicloadiciones 1,3-dipolares con sistemas insaturados, denominados dipolarófilos, experimentando en ellas la pérdida de las cargas formales.

¹⁸ a) A. Padwa, W. H. Pearson en *Synthetic applications of 1,3-dipolar cycloaddition chemistry toward heterocycles and natural products*, John Wiley and Sons, New York, **2003**; b) A. Hassner en *Synthesis of Heterocycles via Cycloadditions*, Springer-Verlag Berlin Heidelberg, **2008**.

¹⁹ *1,3-Dipolar Cycloaddition Chemistry*, Edited by A. Padwa, Wiley Interscience, New York, **1984**.

Aunque hay algunas publicaciones anteriores a 1963 en las que aparece esta reacción,²⁰ lo cierto es que fue Huisgen quien en 1963 reconoció la generalidad de esta transformación creando el concepto de reacción de cicloadición 1,3-dipolar o reacción de Huisgen.²¹



Esquema 1.3. Reacción de cicloadición 1,3-dipolar.

Se pueden distinguir dos tipos de 1,3-dipolos que participan en estas reacciones: los de tipo alilo y los de tipo propargilo/alenilo (Figura 1.2). Los primeros se caracterizan por poseer cuatro electrones en tres orbitales *p* paralelos y perpendiculares al plano del dipolo, y el átomo central puede ser N, O o S. Los de tipo propargilo/alenilo poseen además un orbital π extra ortogonal al orbital molecular del dipolo y en su caso el átomo central sólo puede ser un átomo de nitrógeno.

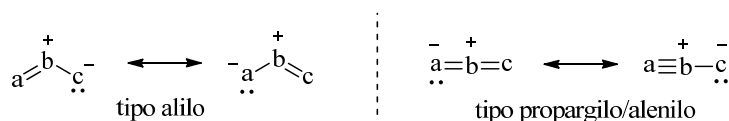


Figura 1.2. Tipos de 1,3-dipolos.

Dentro de los dipolos de tipos propargilo/alenilo se encuentran las azidas descubiertas en 1864 por Greiss²² y muy empleadas en química²³ no sólo en este tipo de reacciones. Las azidas por tanto, son capaces de reaccionar con diferentes dipolarófilos para dar lugar a un anillo de cinco miembros. Así por ejemplo la reacción con alquinos da lugar a triazoles, mientras que con alquenos el producto obtenido es una triazolina.²¹ Sin embargo, en la mayoría de los casos, las triazolinas no son estables como ocurre con los triazoles, y se descomponen eliminando nitrógeno molecular para formar una aziridina o una imina a través de un intermedio zwitteriónico (Esquema 1.4). La formación de uno u otro producto, así como la velocidad de la reacción, dependen de las condiciones y de la naturaleza de los sustituyentes de la azida y del

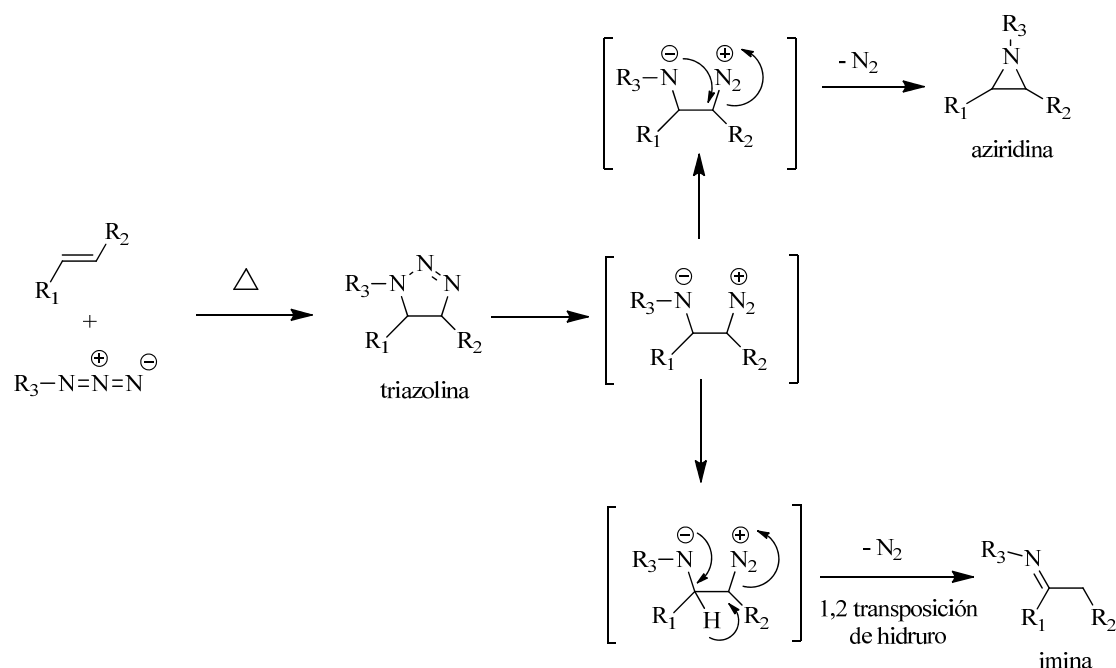
²⁰ a) T. Curtius, *Ber. Dtsch. Chem. Ges.* **1883**, 16, 2230-2231; b) E. Buchner, *Ber. Dtsch. Chem. Ges.* **1888**, 21, 2637-2647; c) E. Beckmann, *Ber. Dtsch. Chem. Ges.* **1890**, 23, 3331-3341; d) K. N. Houk, Y. L. González, *Acc. Chem. Res.* **1995**, 28, 81-90 y referencias citadas.

²¹ a) R. Huisgen, *Angew. Chem.* **1963**, 75, 604-637; b) R. Huisgen, *Angew. Chem. Int. Ed.* **1963**, 2, 565-632.

²² P. Griess, *Philos. Trans. R. Soc. London* **1864**, 154, 667-673.

²³ S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, 44, 5188-5240.

alqueno. Así, por ejemplo, la adición es más rápida con dobles enlaces tensionados y extremadamente lenta con dobles enlaces terminales.²⁴



Esquema 1.4. Reacción de cicloadición 1,3-dipolar azida-alqueno.

La primera vez que se describió la reacción entre una azida y un alqueno fue anterior a Huisgen, en 1912 por Wolf²⁵ y posteriormente Alder y Stein profundizaron en el estudio de la estereoquímica y alcance de la reacción.²⁶ Desde entonces y hasta ahora se ha seguido estudiando esta reacción entre diferentes azidas y olefinas. Ya en 1963 se publicó, por ejemplo, un estudio de la adición de azidas a dobles enlaces no tensionados²⁷ y posteriormente un estudio cinético de la reacción entre azidas aromáticas y norborneno.²⁸ El comportamiento de azidas alquílicas con olefinas sustituidas con grupos electroatrayentes fue también objeto de estudio por parte de los grupos de L'Abbé²⁹ y Carrié.³⁰ La reacción entre trimetilsililazidas y olefinas bicíclicas,³¹ así como la reacción de flouroalquilazidas con alquenos pobres en electrones³² ha sido explorada también describiéndose en cada caso los productos obtenidos.

²⁴ a) R. Huisgen, R. Grashey, J. Sauer en *Chemistry of Alkenes*, Ed. S. Patai, Wiley-Interscience, New York, **1964**, pp. 806-877; b) K. J. Shea, J. S. Kim, *J. Am. Chem. Soc.* **1992**, *114*, 4846-4855.

²⁵ L. Wolff, *Liebigs Ann. Chem.* **1912**, *394*, 23-59.

²⁶ a) K. Alder, G. Stein, *Liebigs Ann. Chem.* **1931**, *485*, 211-222; b) K. Alder, G. Stein, *Liebigs Ann. Chem.* **1933**, *501*, 1-48.

²⁷ P. Scheiner, *Tetrahedron*, **1968**, *24*, 349-356.

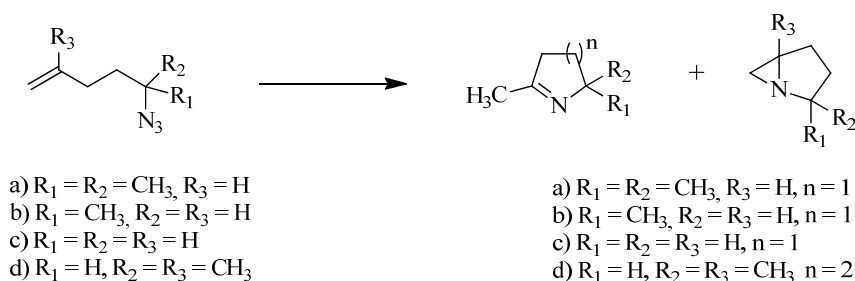
²⁸ P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, G. P. Nowack, *J. Am. Chem. Soc.* **1965**, *87*, 306-311.

²⁹ W. Broeckx, N. Overbergh, C. Samyn, G. Smets, G. L'Abbé, *Tetrahedron*, **1971**, *27*, 3527-3534.

³⁰ M. S. Ouali, M. Vaultier, R. Carrié, *Tetrahedron*, **1980**, *36*, 1821-1828.

³¹ W. R. Peterson, J. B. Arkles, S. S. Washburne, *J. Organomet. Chem.* **1976**, *121*, 285-291.

Especialmente interesante es la versión intramolecular de esta reacción y por ello muchos grupos de investigación han trabajado en este tema. En 1964, Logothetis fue el primero en publicar un artículo sobre la descomposición de azido alquenos (Esquema 1.5).³³ En este trabajo observa que al calentar diferentes azido alquenos a temperaturas entre los 80-320°C empleando diversos disolventes, se forman las correspondientes iminas y aziridinas en diferentes proporciones, pero siempre siendo la imina el producto mayoritario. Además, los autores fueron capaces de aislar dos triazolininas empleando condiciones muy suaves de reacción para posteriormente calentarlas a alta temperatura. De esta manera el resultado fue el mismo que el obtenido al calentar directamente los azido alquenos, por lo que demostraron que la imina y la aziridina se forman por descomposición de la correspondiente triazolinina por eliminación de nitrógeno.



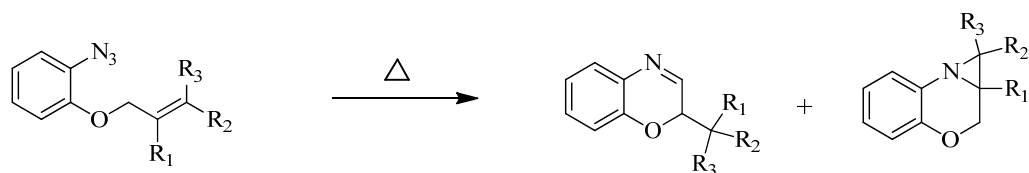
Esquema 1.5. Estudio de la descomposición térmica de azido alquenos (Logothetis, **1965**).³³

Unos años más tarde encontramos otras referencias a la cicloadición 1,3-dipolar azida-alqueno intramolecular. En este caso se trata de la reacción de azidas aromáticas con dobles enlaces unidos a la posición *orto* del anillo (Esquema 1.6).³⁴ En estos artículos se recogen muchos ejemplos de esta reacción en la que los productos son la aziridina y/o imina en diferentes proporciones. Además, el grupo de Smith comprobó que la distribución imina/aziridina es la misma independientemente de la geometría *E/Z* del alqueno, aunque sí que depende del disolvente empleado. La formación de la imina está favorecida al emplear disolventes polares, probablemente porque éstos estabilizan el intermedio zwitteriónico formado tras la descomposición de la triazolinina y hay más tiempo para que se lleve a cabo la transposición 1,2 de hidruro que da lugar a la imina. Así por ejemplo el porcentaje de imina varía en algunos casos desde un 18-19% al emplear decalina, hasta un 53-54% al emplear dimetilacetamida.

³² Q.-R. Sun, Z.-X. Chen, S. Li, Y.-M. Wu, W.-S. Tian, *Chin. J. Chem.* **2008**, 26, 1887-1892.

³³ A. L. Logothetis, *J. Am. Chem. Soc.* **1965**, 87, 749-754.

³⁴ a) R. Fusco, L. Garanti, G. Zecchi, *J. Org. Chem.* **1975**, 40, 1906-1909; b) O. Tsuge, K. Ueno, A. Inaba, *Heterocycles*, **1976**, 4, 1-7; c) P. A. S. Smith, S.-S. P. Chou, *J. Org. Chem.* **1981**, 46, 3970-3977.



a) $R_1 = R_2 = R_3 = H$; b) $R_1 = CH_3$, $R_2 = R_3 = H$; c) $R_1 = R_2 = H$, $R_3 = C_6H_5$; d) $R_1 = R_3 = H$, $R_2 = C_6H_5$; e) $R_1 = R_2 = H$, $R_3 = CH_3$; f) $R_1 = R_3 = H$, $R_2 = CH_3$; g) $R_1 = R_2 = CH_3$, $R_3 = H$; h) $R_1 = R_3 = CH_3$, $R_2 = H$

Esquema 1.6. Cicloadición 1,3-dipolar azida-alqueno intramolecular (Fusco, Tsuge y Smith).³⁴

Desde estas primeras investigaciones se han descrito muchas aplicaciones de la reacción de cicloadición 1,3-dipolar azida-alqueno intramolecular para la síntesis de estructuras muy diversas como: 1,2-dihidroisoquinolinas,³⁵ 2,5-dihidrooxazoles,³⁶ isoindoles e isoquinolinas,³⁷ 1,4-bezodiazepin-5-onas,³⁸ benzazocenos y benzazocenonas,³⁹ benzotiadiazinas, benzotiadiazepinas y benzotiadiazocinas, entre otros.⁴⁰ Igualmente son muchos los ejemplos de síntesis total de alcaloides en los que se emplea esta reacción.⁴¹ Dado por tanto su potencial sintético, esta reacción llamó la atención de nuestro grupo que viene trabajando en la síntesis de heterociclos nitrogenados desde hace varios años.⁴²

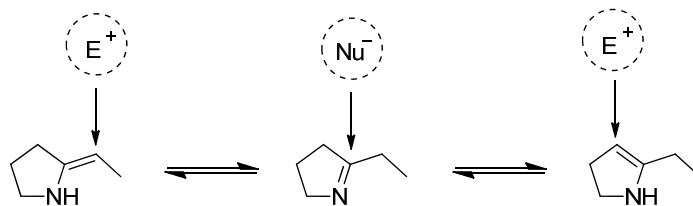


Figura 1.3. Reactividad del enlace C=N de las iminas.

Por otro lado, las características electrónicas del enlace C=N de las iminas, les permite a éstas reaccionar con nucleófilos en el carbono del doble enlace C=N, o con electrófilos en los carbonos en alfa ($C\alpha$) de la imina en su forma tautomérica de enamina (Figura 1.3). Así teniendo en cuenta esta última posibilidad, menos estudiada hasta la fecha, se pensó que iminas

³⁵ J. M. Liu, J. J. Young, Y. J. Li, C. K. Sha, *J. Org. Chem.* **1986**, *51*, 1120-1123.

³⁶ A. Hassner, A. S. Amarasekara, D. Andisik, *J. Org. Chem.* **1988**, *53*, 27-30.

³⁷ B. W.-Q. Hui, S. Chiba, *Org. Lett.* **2009**, *11*, 729-732.

³⁸ V. Santagada, E. Perissutti, F. Fiorino, B. Vivencio, G. Caliendo, *Tetrahedron Lett.* **2001**, *42*, 2397-2400.

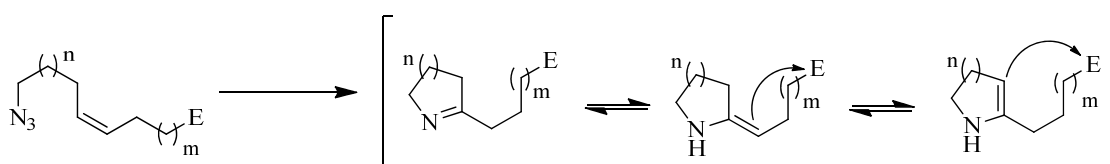
³⁹ a) M. A. Ciufolini, M. Chen, D. P. Lovett, M. V. Deaton, *Tetrahedron Lett.* **1997**, *38*, 4355-4358; b) R. Ducray, N. Cramer, M. A. Ciufolini, *Tetrahedron Lett.* **2001**, *42*, 9175-9178.

⁴⁰ N. Patel, C. S. Chambers, K. Hemming, *Synlett*, **2009**, *18*, 3043-3047.

⁴¹ La aplicación de la reacción de cicloadición 1,3-dipolar azida-alqueno en la síntesis total de productos naturales aparece comentada en la introducción del capítulo 3 de esta tesis.

⁴² a) F. Sánchez-Sancho, E. Mann, B. Herradón, *Synlett*, **2000**, 509-513; b) F. Sánchez-Sancho, E. Mann, B. Herradón, *Adv. Synth. Catal.* **2001**, *343*, 360-368; c) A. Salgado, E. Mann, F. Sánchez-Sancho, B. Herradón, *Heterocycles*, **2003**, *60*, 57-71; d) R. Chicharro, M. Alonso, M. T. Mazo, V. J. Arán, B. Herradón, *ChemMedChem*, **2006**, *1*, 710-714; e) R. Chicharro, M. Alonso, V. J. Arán, B. Herradón, *Tetrahedron Lett.* **2008**, *49*, 2275-2279.

obtenidas mediante cicloadición 1,3-dipolar azida-alqueno intramolecular podrían reaccionar con un grupo electrófilo situado a una distancia adecuada en la misma molécula a través de las enaminas correspondientes (Esquema 1.7). De esta manera nos propusimos sintetizar azido alquenos convenientemente funcionalizados para obtener policiclos nitrogenados de manera sencilla y directa mediante una reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición de enamina. Así mismo nos planteamos aplicar esta reacción de cicloadición en la síntesis total de alcaloides, un campo donde nuestro grupo también tiene experiencia previa.⁴³ A continuación se recogen más en detalle los objetivos de esta tesis doctoral.



Esquema 1.7. Planteamiento de la reacción en cascada de cicloadición 1,3-dipolar azida-alqueno/adición de enamina.

1.2.-OBJETIVOS.

Los objetivos planteados en esta tesis son:

1.- Poner a punto una ruta de síntesis para la preparación de azido alquenos con los que llevar a cabo la reacción de cicloadición 1,3-dipolar azida-alqueno intramolecular para la síntesis de iminas cíclicas de tipo 1-pirrolinas y 1-piperideinas.

2.- Estudiar la reactividad de las iminas cíclicas con diferentes electrófilos y desarrollar una reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición de enamina para la preparación de policiclos nitrogenados de manera sencilla y directa.

3.- Emplear la reacción de cicloadición 1,3-dipolar azida-alqueno en la síntesis total de alcaloides.

⁴³ F. Sánchez-Sancho, B. Herradón, *Tetrahedron: Asymmetry*, **1998**, 9, 1951-1965.

Los resultados derivados de la consecución de estos objetivos planteados se recogen en la presente memoria de tesis doctoral estructurados en tres capítulos:

- *Reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición de enamina*
- *Aproximación a la síntesis de alcaloides de Lycopodium*
- *Síntesis total de la amforoginina C*

Al final de cada uno de ellos se encuentra la parte experimental con los procedimientos para la preparación de los diferentes compuestos, así como la caracterización de cada uno de ellos mediante ^1H -RMN, ^{13}C -RMN, HRMS-ESI, IR, punto de fusión para los productos sólidos a temperatura ambiente y rotación óptica para los productos enantioméricamente puros.

Dado que gran cantidad de estos compuestos ya han sido publicados en revistas internacionales se ha mantenido el formato en inglés para toda la parte experimental facilitando así también la redacción de futuras publicaciones. En el capítulo 5 se exponen a modo de resumen las conclusiones del trabajo realizado. Finalmente en el anexo I se incluyen los espectros de ^1H -RMN de los compuestos más representativos; en el anexo II los datos correspondientes a las estructuras cristalinas resueltas por difracción de rayos X; y en el anexo III las publicaciones derivadas de este trabajo.

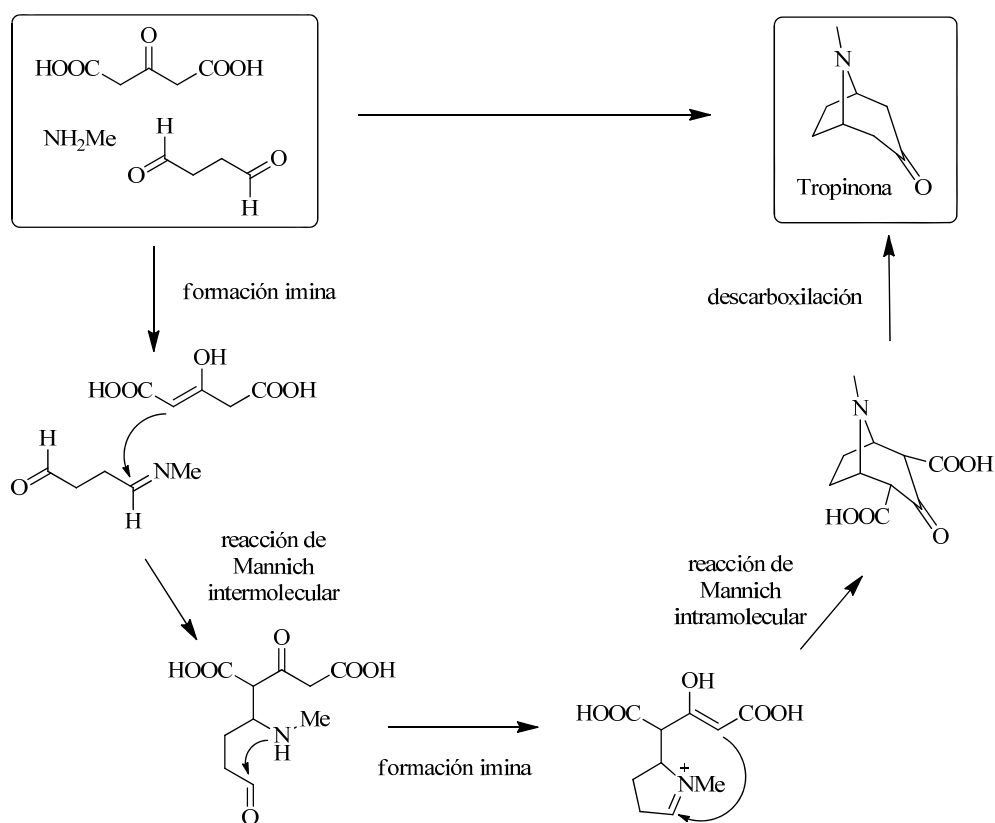
Capítulo 2

**REACCIÓN EN CASCADA DE CICLOADICIÓN 1,3-DIPOLAR
AZIDA-ALQUENO INTRAMOLECULAR/ADICIÓN DE ENAMINA**

2.1.-INTRODUCCIÓN Y ANTECEDENTES.

2.1.1.- Reacciones en cascada.

El desarrollo de nuevas reacciones en cascada ha suscitado mucho interés en la química orgánica durante los últimos años.¹ Este tipo de reacciones presentan muchas ventajas como son: reducción de los pasos de reacción y purificaciones,² eliminación de etapas de protección/desprotección, ahorro de reactivos, disolventes, energía, etc. Además, en la mayoría de los casos, permiten la formación de varios enlaces nuevos de manera estereoselectiva en una única etapa, aumentando así la complejidad estructural de la molécula. Todo ello hace de las reacciones en cascada un excelente método para la síntesis de sistemas policíclicos y, especialmente, de heterociclos.³



Esquema 2.1. Síntesis de la tropinona (Robinson, 1917).⁴

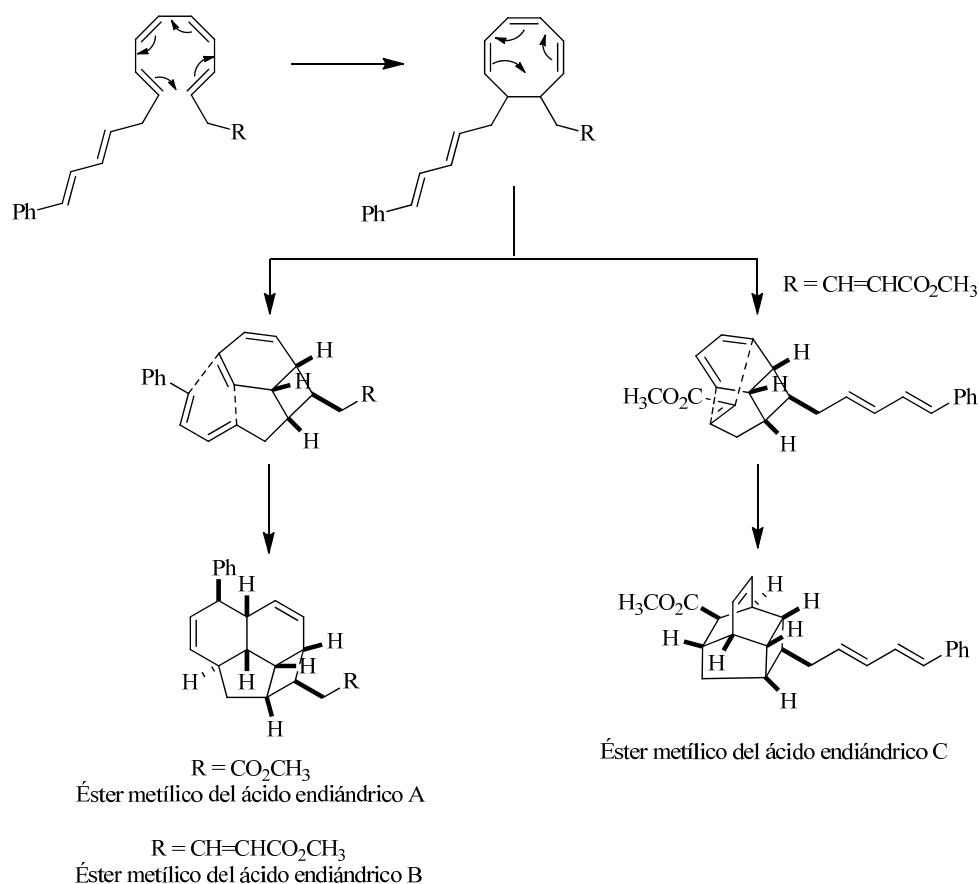
¹ a) L. F. Tietze, G. Brasche, K. Gericke, en *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**; b) K. C. Nicolau, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int. Ed.* **2006**, *45*, 7134-7186; c) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.* **2007**, *46*, 1570-1581.

² a) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40-49; b) R. A. Sheldon, *Chem. Soc. Rev.* **2012**, *41*, 1437-1451.

³ a) M. Ihara, *Arkivoc*, **2006**, *7*, 416-438; b) E. A. Anderson, *Org. Biomol. Chem.* **2011**, *9*, 3997-4006; c) L.-Q. Lu, J.-R. Chen, W.-J. Xiao, *Acc. Chem. Res.* **2012**, *45*, 1278-1293.

Desde hace ya muchos años se vienen empleando estas reacciones en química orgánica y tal vez uno de los primeros ejemplos, ya clásico, sea la síntesis de la tropinona de Robinson (Esquema 2.1).⁴ En esta investigación, partiendo de metilamina, succinaldehído y el ácido 3-oxopentandienoico se sintetiza este producto natural a través de una doble reacción de Mannich y descarboxilación que tienen lugar en una sola etapa.

Otro clásico ejemplo de reacción en cascada lo encontramos en la síntesis de los ácidos endiátricos de Nicolau (Esquema 2.2).⁵ En esta síntesis a partir de un sistema poliénico construye toda la familia de ácidos endiátricos A-G. La síntesis transcurre a través de dos reacciones pericíclicas de electrociclación y una cicloadición [4+2] del ciclobutano intermedio construyéndose en una sola etapa los ésteres metílicos de los ácidos endiátricos A, B y C y siendo el resto de ácidos, intermedios que pueden aislarse bajo las condiciones adecuadas.



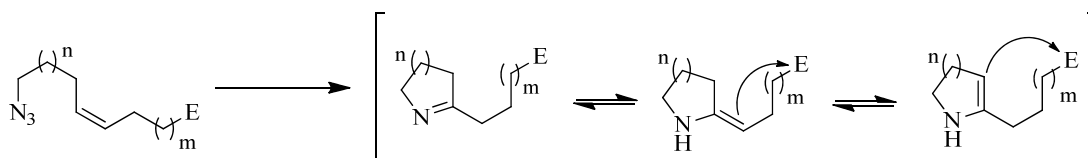
Esquema 2.2. Síntesis de los ácidos endiátricos B y C (Nicolau, 1982).⁵

⁴ R. Robinson, *J. Chem. Soc. Trans.* **1917**, 762-768.

⁵ a) K. C. Nicolau, N. A. Petasis, R. E. Zipkin, J. Uenishi, *J. Am. Chem. Soc.* **1982**, *104*, 5555-5557; b) K. C. Nicolau, N. A. Petasis, J. Uenishi, R. E. Zipkin, *J. Am. Chem. Soc.* **1982**, *104*, 5557-5558; c) K. C. Nicolau, R. E. Zipkin, N. A. Petasis, *J. Am. Chem. Soc.* **1982**, *104*, 5558-5560; d) K. C. Nicolau, N. A. Petasis, R. E. Zipkin, *J. Am. Chem. Soc.* **1982**, *104*, 5560-5562.

Además de estos dos clásicos ejemplos de reacción en cascada, en la literatura se pueden encontrar muchas referencias a este tipo de reacciones ya que son muchos los grupos de investigación que han centrado su interés en ellas dadas las ventajas ya comentadas. Alentados por estos interesantes precedentes nos propusimos también nosotros diseñar una reacción en cascada para la síntesis de policiclos nitrogenados de manera sencilla y directa.

Como se comentó en la introducción de esta tesis, las iminas pueden reaccionar con nucleófilos en el carbono del doble enlace $C=N$, o con electrófilos en los carbonos en alfa ($C\alpha$) de la imina en su forma tautomérica de enamina. En base a esta reactividad, se planteó la posibilidad de llevar a cabo una reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular, para la síntesis de iminas cíclicas, seguida de la reacción de la enamina endo o exocíclica, con diferentes electrófilos situados en la misma molécula en la posición adecuada para poder formar policiclos nitrogenados en una sola etapa de reacción (Esquema 2.3).



Esquema 2.3. Reacción en cascada planteada para la síntesis de policiclos nitrogenados.

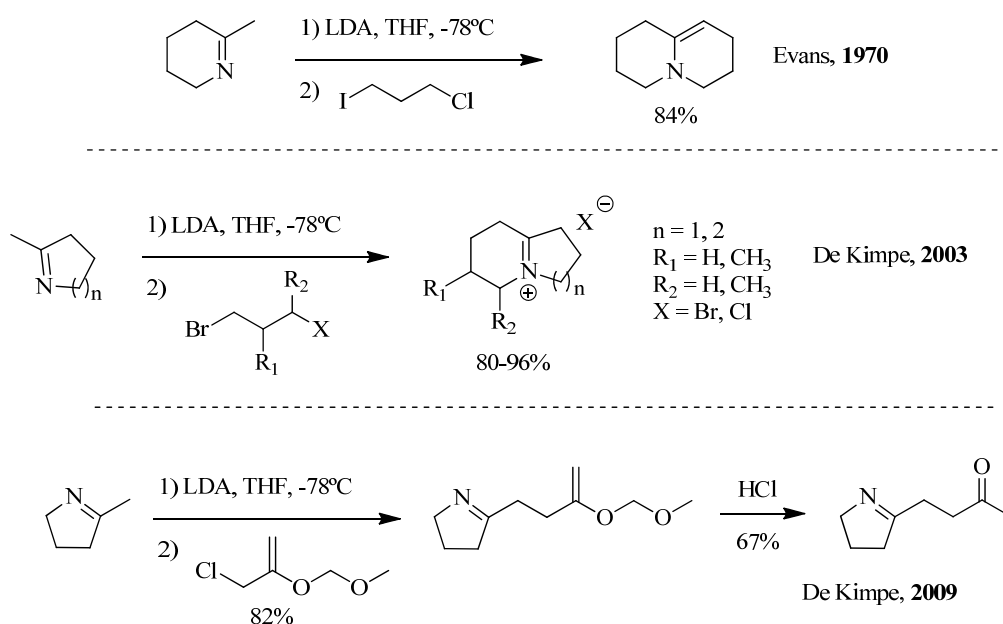
2.1.2.- Antecedentes de la reacción de iminas cíclicas con electrófilos.

En la literatura únicamente se encuentran algunos precedentes sobre la reacción de iminas cíclicas con electrófilos. Entre ellos hay algunos ejemplos de reacciones de metaloenaminas cíclicas con halogenuros de alquilo (Esquema 2.4). Así, Evans⁶ publicó la reacción de iminas cíclicas desprotonadas por LDA con 1-cloro-3-yodopropano para la síntesis de enaminas cíclicas. Unas reacciones muy similares son las descritas por el grupo de De Kimpe. En este caso emplean también LDA como base y hacen reaccionar las metaloenaminas con dihalogenuros de alquilo para la formación de indolizidinas y quinolizidinas;⁷ o con 3-cloro-2-(metoximetiloxi)-1-propeno para obtener productos que tras hidrólisis conducen a 2-(3-oxobutil)-1-pirrolinas.⁸

⁶ D. A. Evans, *J. Am. Chem. Soc.* **1970**, 92, 7593-7595.

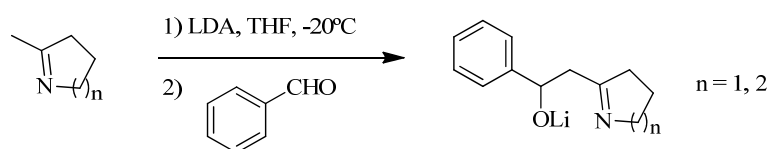
⁷ K. A. Tehrani, M. D'hooghe, N. De Kimpe, *Tetrahedron*, **2003**, 59, 3099-3108.

⁸ M. D'hooghe, K. A. Tehrani, N. De Kimpe, *Tetrahedron*, **2009**, 65, 3753-3756.



Esquema 2.4. Reacción de metaloenaminas cíclicas con halogenuros de alquilo.^{6,7,8}

También está descrita la reacción entre iminas desprotonadas con LDA y benzaldehído, reacción empleada por Vaultier en la síntesis de la nor-sedamine (Esquema 2.5).⁹

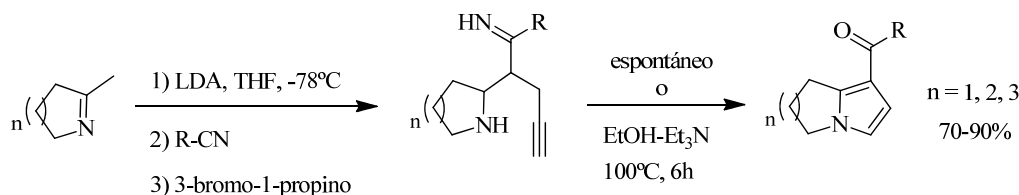


Esquema 2.5. Reacción de iminas cíclicas con benzaldehído (Vaultier, 1989).⁹

Otro interesante ejemplo de la adición de iminas cíclicas a electrófilos lo encontramos en un trabajo del grupo de Barluenga para la síntesis de pirroles (Esquema 2.6).¹⁰ Dicha metodología se basa en la adición de metaloenaminas a nitrilos atrapando el resultante anión de diazapentadienilo formado con 3-bromo-1-propino. Finalmente se lleva a cabo una reacción de cicloaminación para obtener los productos finales, los pirroles.

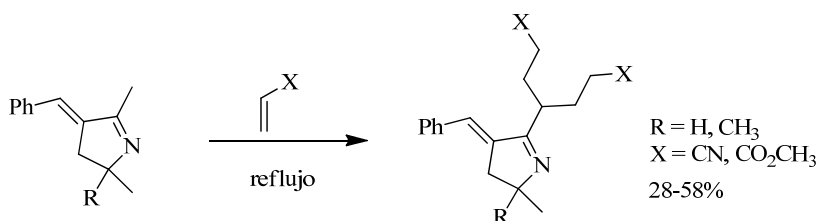
⁹ P.-J. Tirel, M. Vaultier, R. Carrié, *Tetrahedron Lett.* **1989**, 30, 1947-1950.

¹⁰ J. Barluenga, M. Tomás, V. Kouznetsov, E. Rubio, *J. Chem. Soc. Chem. Commun.* **1992**, 1419-1420.



Esquema 2.6. Reacción de iminas cíclicas con nitrilos (Barluenga, **1992**).¹⁰

En cuanto a la reacción de iminas cíclicas con aceptores de Michael como electrófilos únicamente hay dos precedentes y en ambos casos se trata de una reacción intramolecular. El primero es del grupo de Kim en el que estudian la adición de acrilonitrilo y acrilato de metilo a una serie de derivados de pirrolina (Esquema 2.7).¹¹ El producto que aíslan es el resultante de una doble adición aunque los resultados no superan en ninguno de los ejemplos el 60%.



Esquema 2.7. Reacción de iminas cíclicas con acrilonitrilo y acrilato de metilo (Kim, **2005**).¹¹

El otro ejemplo es un trabajo de Movassaghi sobre la adición de iminas cíclicas a enonas cíclicas para la formación de imino alcoholes (Esquema 2.8).¹² Este proceso tiene lugar a través de la desprotonación de la imina con n-BuLi y adición 1,4 de la metaloenamina a la enona para formar una ceto imina que sigue reaccionando mediante la adición de la enamina endocíclica a la cetona.¹³ De esta manera se preparan una serie de imino alcoholes de forma estereoselectiva. Esta metodología fue empleada después con éxito por el grupo para completar la síntesis total de los alcaloides (-)-galbulimima 13 (GB-13)¹⁴ e himandrina¹⁵ que poseen en su estructura uno de estos imino alcoholes (Esquema 2.8).

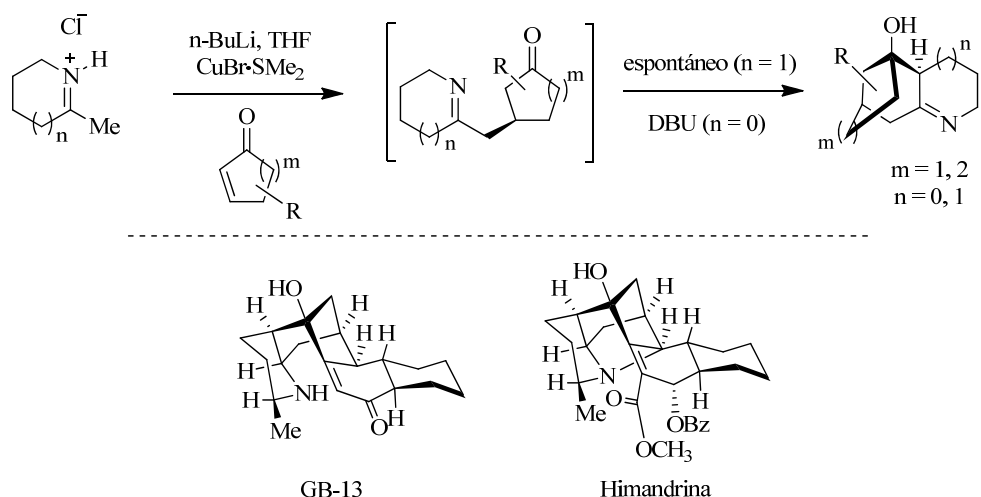
¹¹ M. J. Lee, K. Y. Lee, D. Y. Park, J. N. Kim, *Bull. Korean Chem.* **2005**, 26, 1281-1285.

¹² M. Movassaghi, B. Chen, *Angew. Chem. Int. Ed.* **2007**, 46, 565-568.

¹³ Esta adición 1,2 de la enamina endocíclica a la cetona es el primer ejemplo de adición intramolecular de una imina cíclica descrito.

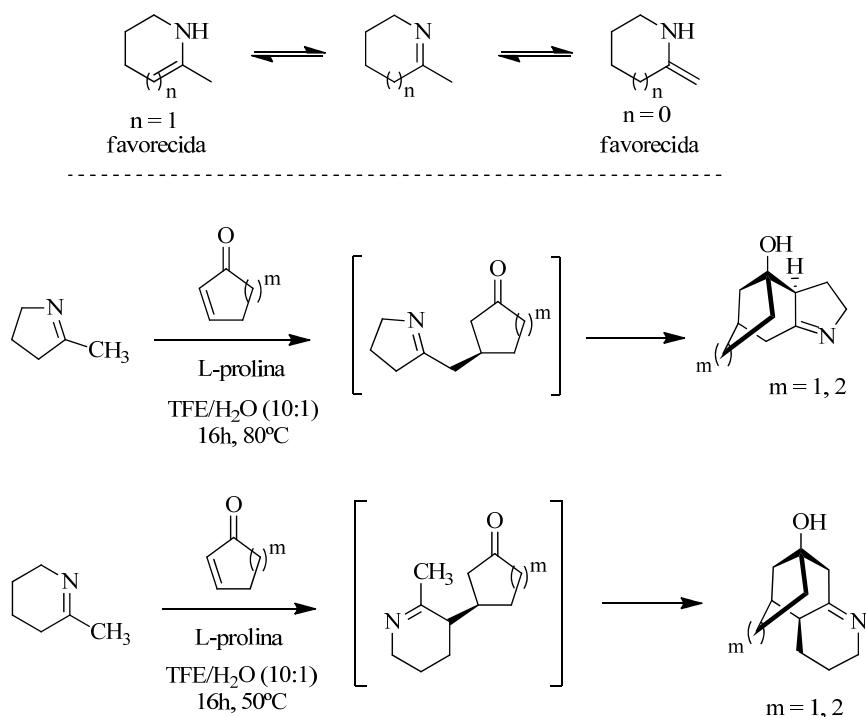
¹⁴ M. Movassaghi, D. K. Hunt, M. Tjandra, *J. Am. Chem. Soc.* **2006**, 128, 8126-8127.

¹⁵ M. Movassaghi, M. Tjandra, J. Qi, *J. Am. Chem. Soc.* **2009**, 131, 9648-9650.



Esquema 2.8. Síntesis de imino alcoholes (Movassaghi, **2007**).¹²

En este trabajo de Movassaghi se estudia además el equilibrio imina/enamina, observándose que en las piperideinas está más favorecida la enamina endocíclica; mientras que en las pirrolinas la enamina exocíclica está favorecida (Esquema 2.9). Basándose en estos resultados y aprovechando la diferente reactividad de las enaminas endo y exocíclicas, llevaron a cabo la reacción de doble adición a las enonas con las iminas cíclicas directamente, empleando prolina como catalizador, en lugar de emplear las correspondientes metaloenaminas (Esquema 2.9).



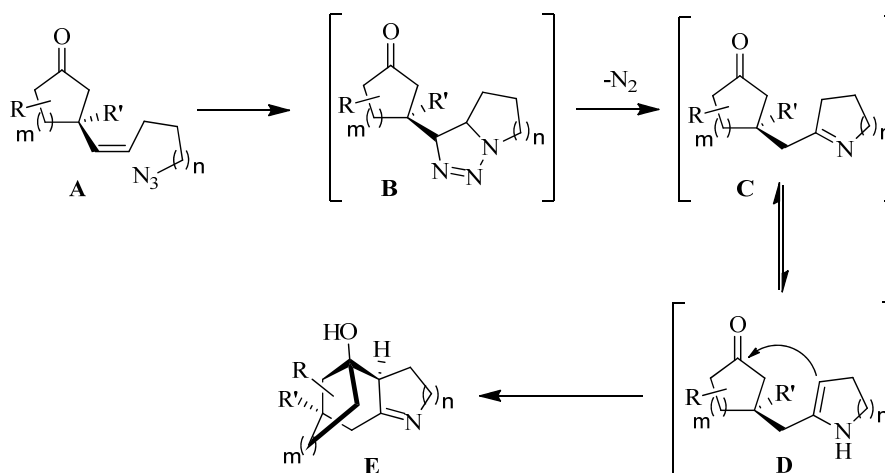
Esquema 2.9. Reacción de adición de iminas cíclicas a enonas cíclicas (Movassaghi, **2007**).¹²

2.2.- EXPOSICIÓN DE RESULTADOS.

2.2.1- Síntesis de imino alcoholes policíclicos mediante reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición de enamina.

2.2.1.1.- Síntesis de imino alcoholes tricíclicos.

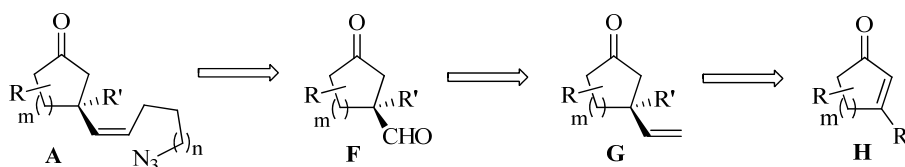
Tomando como punto de partida el trabajo de Movassaghi en el que es posible la adición de iminas cíclicas sobre enonas,¹² nos planteamos la posibilidad de sintetizar imino alcoholes mediante una reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición 1,2 de enamina (Esquema 2.10). Para ello se pensó en preparar compuestos con la estructura genérica del azido alqueno **A**, que tras una reacción de cicloadición 1,3-dipolar azida-alqueno intramolecular y descomposición de la triazolina formada **B**, podrían dar lugar a la imina cíclica **C**. Seguidamente la enamina endocíclica en equilibrio tautomérico con dicha imina (**D**) podría reaccionar con la cetona mediante una adición 1,2 para formar en un solo paso el correspondiente imino alcohol **E**.



Esquema 2.10. Reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición de enamina.

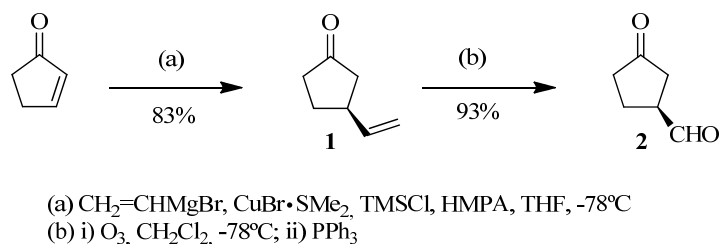
Con esta idea en mente se planteó una sencilla síntesis de los azido alquenos de partida **A** mediante reacción de Wittig de aldehídos con estructura **F** con una sal de fosfonio convenientemente funcionalizada (Esquema 2.11).¹⁶ A su vez los aldehídos serían el resultado de una ozonolisis del doble enlace terminal de las cetonas **G**. Finalmente estos ceto alquenos se sintetizarían a partir de enonas **H** por una adición 1,4 de bromuro de vinilmagnesio.

¹⁶ S. Kim, Y. M. Lee, J. Lee, T. Lee, Y. Fu, Y. Song, J. Cho, D. Kim, *J. Org. Chem.* **2007**, 72, 4886-4891.



Esquema 2.11. Retrosíntesis de los azido alquenos.

En primer lugar se escogió como compuesto modelo la 2-ciclopentenona y se hizo reaccionar con bromuro de vinilmagnesio en presencia de sales de cobre para favorecer la adición conjugada 1,4 frente a la adición 1,2.¹⁷ Así se obtuvo el compuesto **1** con un 83% de rendimiento y de manera totalmente regioselectiva (Esquema 2.12). A continuación se sometió el alqueno a ozonolisis¹⁸ para llevar a cabo una ruptura oxidativa del doble enlace terminal. Para ello se burbujeó ozono sobre una disolución del compuesto en diclorometano a -78°C hasta la aparición de un ligero tono azul, indicativo de la finalización de la reacción. De esta manera se obtuvo el aldehído correspondiente **2** con muy buen rendimiento.



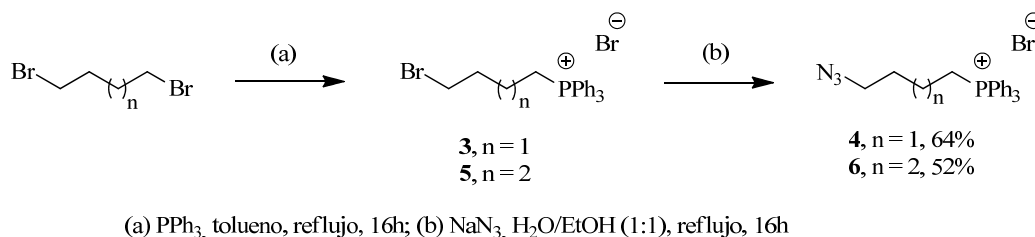
Esquema 2.12. Síntesis del compuesto **2**.

Para funcionalizar convenientemente la posición 3 de la cetona se empleó una reacción de Wittig con las sales de fosfonio **4** y **6** descritas ya anteriormente en la literatura por Vaultier¹⁹ y preparadas a partir de los correspondientes dibromuros mediante doble reacción de sustitución nucleófila con trifenilfosfina en primer caso, y con azida sódica a continuación (Esquema 2.13). De esta manera se pudieron obtener las sales de fosfonio **4** y **6** en escala multigramo. Además estas sales de fosfonio pueden ser almacenadas durante meses a temperatura ambiente.

¹⁷ P. Perlmutter en *Conjugate Addition Reactions in Organic Synthesis*, Tetrahedron Organic Chemistry Series 9, Pergamon, Oxford, **1992**.

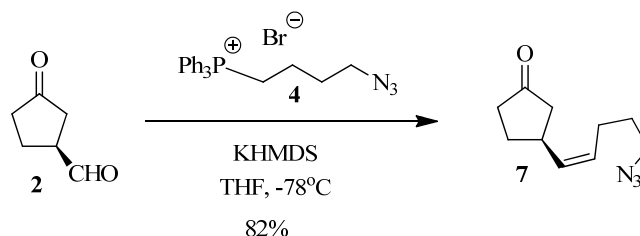
¹⁸ C. Hurries, *Liebigs Ann. Chem.* **1905**, 343, 311-344.

¹⁹ A. Chhen, M. Vaultier, R. Carrié, *Tetrahedron Lett.* **1989**, 30, 4953-4956.



Esquema 2.13. Síntesis de las sales de fosfonio **4** y **6**.

La reacción de Wittig²⁰ del aldehído **2** con la sal de fosfonio **4** empleando KHMDS como base,²¹ condujo al alqueno **7** con buen rendimiento (Esquema 2.14). En este caso como es de esperar para esta reacción con iluros de fósforo no estabilizados y a baja temperatura, el producto formado es el alqueno Z.

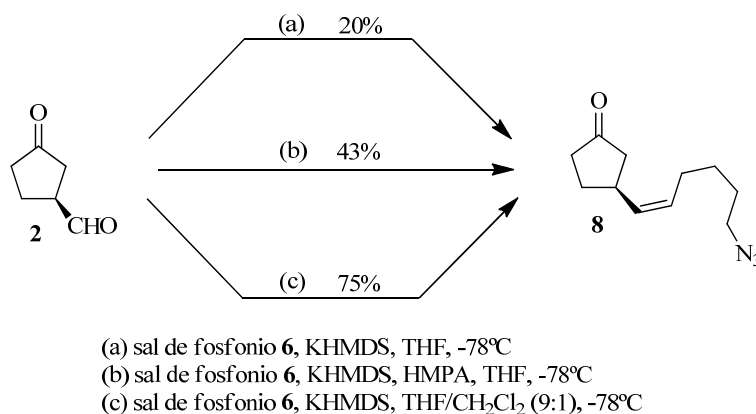


Esquema 2.14. Síntesis del compuesto **7**.

Sin embargo, la reacción del mismo aldehído **2** bajo estas condiciones de reacción con la sal de fosfonio **6** condujo al correspondiente alqueno **8** con muy bajo rendimiento (Esquema 2.15). Esto es debido a la baja solubilidad de la sal de fosfonio en THF a baja temperatura. En la síntesis de la criptopleurina, Kim y colaboradores describen el mismo problema al emplear esta sal de fosfonio en una reacción de Wittig y por eso emplean HMPA para ayudar a solubilizar el iluro de fósforo aumentando así el rendimiento.¹⁶ En nuestro caso, el empleo de HMPA produjo una mejora en el rendimiento, pero únicamente se alcanzó un 43%. Fue al adicionar diclorometano como codisolvente en proporción THF/ CH_2Cl_2 (9:1) cuando sí se obtuvo un buen rendimiento del 75%. El procedimiento se llevó a cabo disolviendo primero la sal de fosfonio en CH_2Cl_2 para luego añadir el THF. Seguidamente y una vez enfriada la disolución a -78°C , se adicionó la base. De esta manera toda la sal de fosfonio está disuelta y puede reaccionar.

²⁰ a) G. Wittig, G. Geissler, *Liebigs Ann.* **1953**, 44-57; b) G. Wittig, U. Schöllkopf, *Chem. Ber.* **1954**, 87, 1318-1330; c) G. Wittig, W. Haag, *Chem. Ber.* **1955**, 88, 1654-1666; d) M. Edmonds, A. Abell en *Modern Carbonyl Olefination* Ed. T. Takeda, Wiley-VCH, **2004**.

²¹ Se realizó la reacción empleando KHMDS como base ya que es lo descrito por Vaultier al emplear esta sal de fosfonio.



Esquema 2.15. Síntesis del compuesto **8**.

Una vez sintetizados los azido alquenos modelo se pasó a explorar la reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición de enamina. Se escogió como disolvente la DMF empleada en muchas ocasiones para esta reacción de cicloadición ya que permite alcanzar temperaturas elevadas.²² Además es un disolvente polar y que por tanto favorece la formación de la imina frente a la aziridina.²³ Así, al calentar a 120°C en un tubo sellado una disolución del compuesto **8** en DMF durante 14 horas se obtuvo el correspondiente imino alcohol **9** con un rendimiento del 64% como un único diastereoisómero (Esquema 2.16).²⁴ A continuación en un intento de reducir el tiempo de reacción se empleó radiación de microondas y se obtuvo el imino alcohol con un rendimiento similar en tan sólo 3 horas.

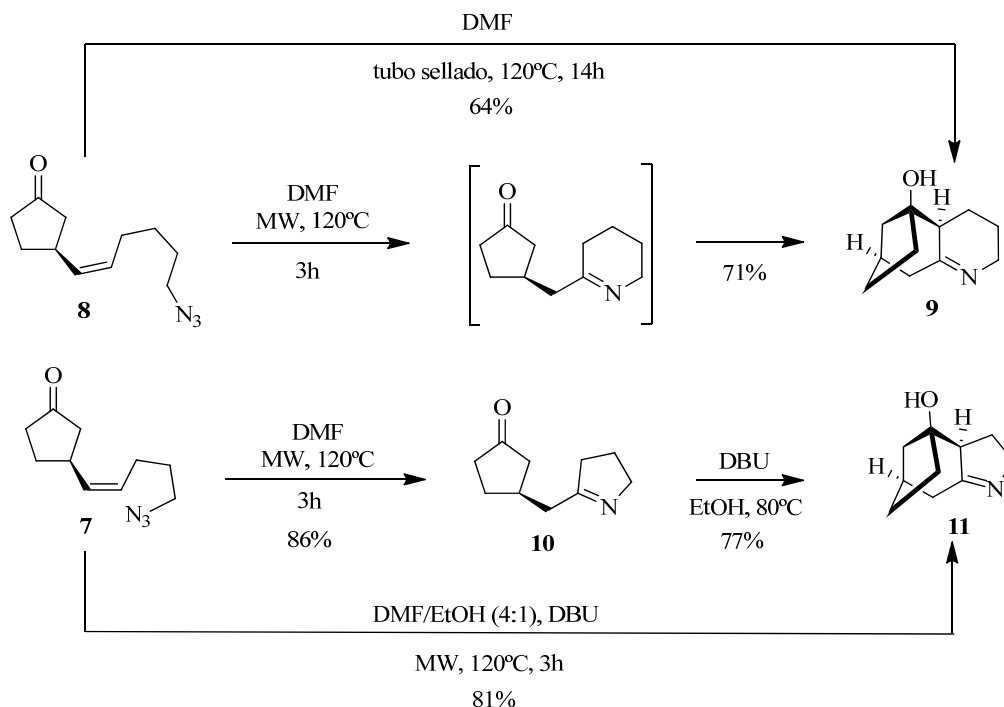
Sin embargo, al aplicar estas mismas condiciones de reacción con el compuesto **7** no se obtuvo el deseado imino alcohol, sino la ceto imina intermedia **10** con buen rendimiento.²⁵ Posteriormente dicha imina se sometió a las condiciones descritas por Movassaghi para la adición 1,2 de la enamina a la cetona.¹² De este modo, por tratamiento con DBU en etanol a reflujo se sintetizó el correspondiente imino alcohol **11** con buen rendimiento y con un total diastereocontrol. Para poder obtener el imino alcohol en una sola etapa desde el compuesto **8**, se hizo reaccionar a éste con DBU en DMF a 120°C en el microondas, pero el resultado fue de nuevo la ceto imina intermedia. Se probó entonces la reacción con DBU en una mezcla de DMF/EtOH (4:1) durante 3 horas en el microondas y en ese caso sí, se obtuvo el imino alcohol en una sólo etapa y con buen rendimiento.

²² Algunos ejemplos de cicloadiciones 1,3-dipolares donde se emplea DMF como disolvente: a) R. B. Bennett III, J. R. Choi, W. D. Montgomery, J. K. Cha, *J. Am. Chem. Soc.* **1989**, *111*, 2580-2582; b) R. B. Bennett III, J. K. Cha, *Tetrahedron Lett.* **1990**, *31*, 5437-5440; c) J.-R. Choi, S. Han, J. K. Cha, *Tetrahedron Lett.* **1991**, *32*, 6469-6472; d) V. Santagada, E. Perissutti, F. Foirino, B. Vivencio, G. Caliendo, *Tetrahedron Lett.* **2001**, *42*, 2397-2400.

²³ P. A. S. Smith, S.-S. P. Chou, *J. Org. Chem.* **1981**, *46*, 3970-3977.

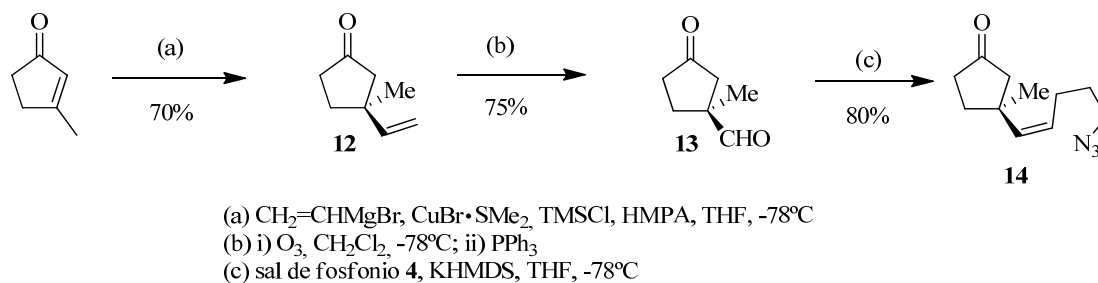
²⁴ Todos los datos espectroscópicos del compuesto coinciden con los ya descritos por Movassaghi.

²⁵ Movassaghi ya observó esta falta de reactividad de las pirrolinas y la necesidad de emplear DBU en etanol a 80°C para que tenga lugar la adición de la enamina.



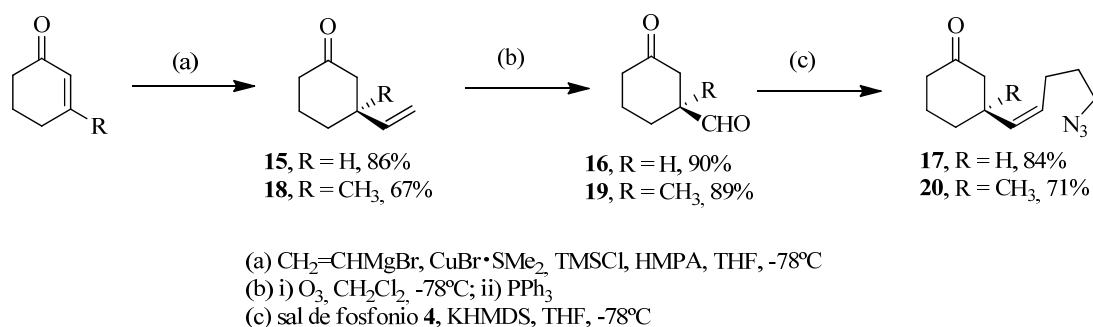
Esquema 2.16. Síntesis de los imino alcoholes **9** y **11**.

Una vez optimizadas las condiciones de reacción y con la intención de conocer la generalidad de la reacción, preparamos otros azido alquenos partiendo de varias cetonas cíclicas α,β -insaturadas. En primer lugar se prepararon los azido alquenos con la sal de fosfonio **4** empleando la ruta de síntesis ya puesta a punto de adición de magnesiano, ozonolisis y reacción de Wittig. Así, por reacción de la 3-metil-2-ciclopentenona con bromuro de vinilmagnesio se obtuvo el producto **12** que tras ozonolisis permitió obtener el aldehído **13** (Esquema 2.17). Finalmente la reacción de Wittig con la sal de fosfonio **4** condujo al azido alqueno **14**.



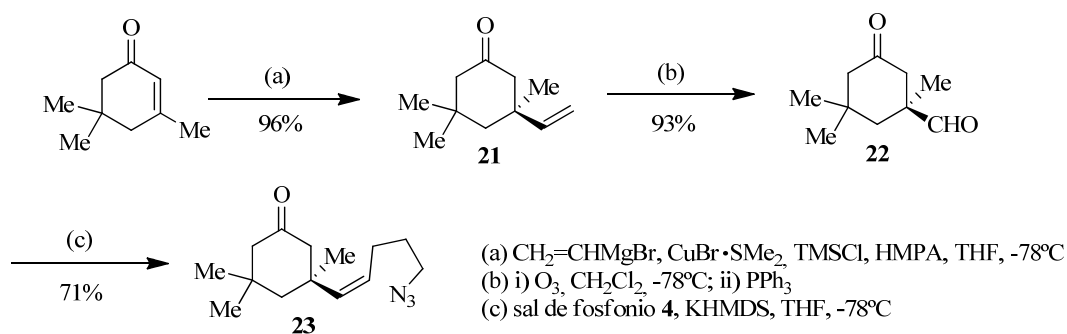
Esquema 2.17. Síntesis del compuesto **14**.

Las mismas condiciones de reacción se emplearon con la 2-ciclohexenona y la 3-metil-2-ciclohexenona para obtener los azido alquenos **17** y **20** respectivamente (Esquema 2.18).



Esquema 2.18. Síntesis de los compuestos **17** y **20**.

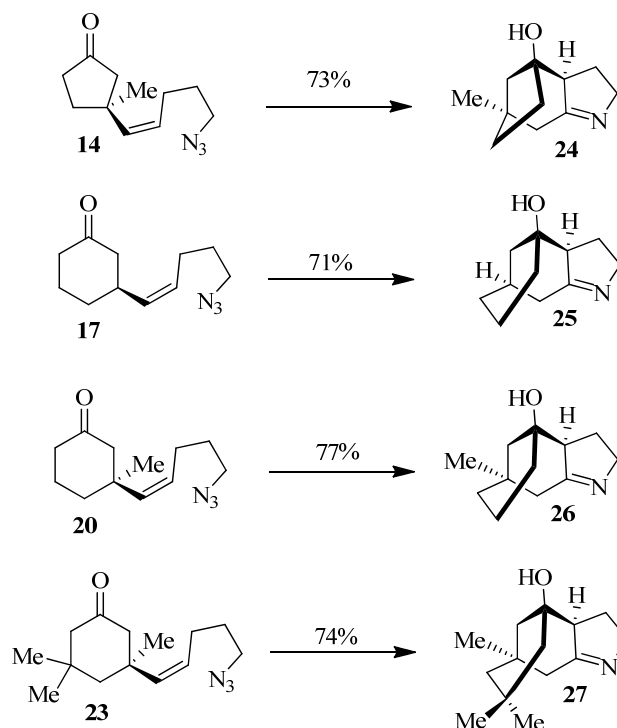
Por último se pensó en emplear también la isoforona, una cetona cíclica α,β -insaturada con más sustituyentes para estudiar si estos grupos metilo dificultan o no la formación del imino alcohol. La síntesis del azido alqueno **23** se realizó mediante la misma metodología obteniendo buenos rendimientos en todas las etapas (Esquema 2.19).



Esquema 2.19. Síntesis del compuesto **23**.

La ciclación de estos otros cuatro azido alquenos se realizó aplicando las condiciones anteriormente optimizadas, empleando DBU en una mezcla DMF/EtOH (4:1) bajo radiación de microondas a 120°C durante 3 horas. En todos los casos se obtuvieron los imino alcoholes correspondientes de manera totalmente diastereoselectiva y con muy buenos rendimientos (Esquema 2.20).²⁶ Los rendimientos fueron los mismos en la formación de los sistemas tricíclicos de 5-azatriciclo[6.2.1.0^{2,6}] (a partir de las ciclopentanonas) y de 5-azatriciclo[6.3.1.0^{2,6}] (a partir de las ciclohexanonas). Además los grupos metilo en las posiciones 3 y 5 de las cetonas no parecen dificultar la reacción en cascada ya que los tiempos de reacción y los rendimientos son muy similares en todos los casos.

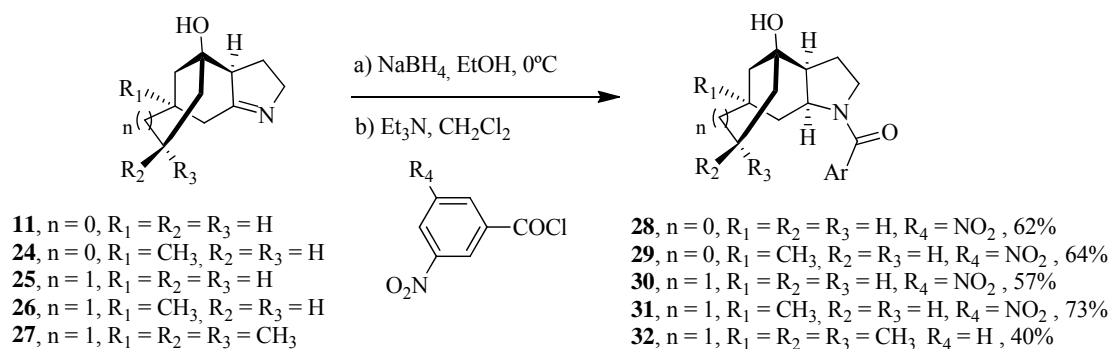
²⁶ En todos los casos se comprobó que el empleo de DBU y etanol era necesario ya que al calentar los azido alquenos en DMF , únicamente se obtuvieron las ceto iminas correspondientes, pero no se producía la adición 1,2 sobre la cetona.



DBU, DMF/EtOH (4:1), 120°C, MW, 3h

Esquema 2.20. Síntesis de los imino alcoholes **24**, **25**, **26** y **27**.

La posterior reducción de estos imino alcoholes se llevó a cabo empleando NaBH_4 como fuente de hidruro ya que este reactivo es el descrito por Movassaghi para reducir estas iminas de manera estereoselectiva (Esquema 2.21).¹² Seguidamente las correspondientes aminas se acilaron con un cloruro de ácido para obtener de esa manera las amidas **28** a **32** como sólidos blancos en todos los casos. Esto permitió además confirmar la estereoquímica de los imino alcoholes mediante el estudio de difracción de rayos X del compuesto **29** (Figura 2.1).²⁷



Esquema 2.21. Síntesis de las amidas aromáticas **28** a **32**.

²⁷ Los datos de difracción de rayos X del compuesto **29** se encuentran en el anexo II.

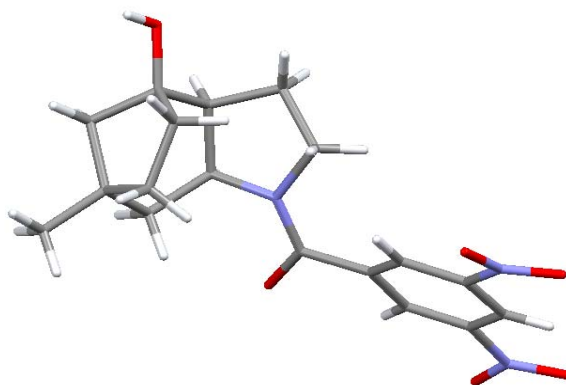
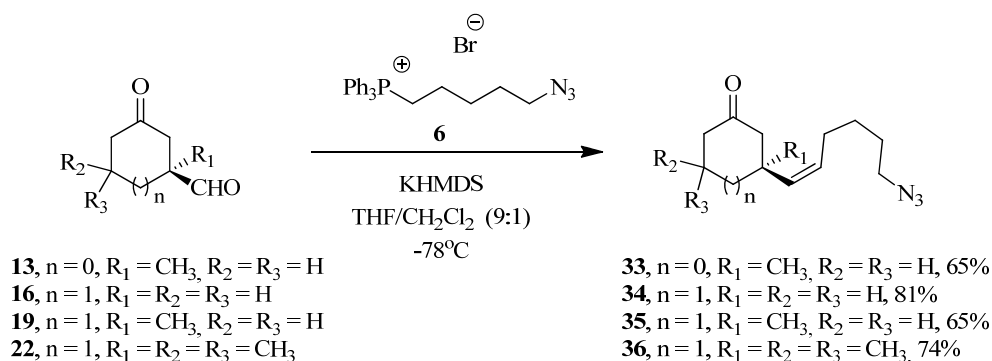


Figura 2.1. Estructura de rayos X del compuesto **29**.

Para la síntesis de los imino alcoholes policíclicos análogos con un anillo de piperideina en su estructura se sintetizaron también los correspondientes azido alquenos empleando en este caso la sal de fosfonio **6** en las condiciones puestas a punto anteriormente y partiendo de los aldehídos ya sintetizados **13**, **16**, **19** y **22** (Esquema 2.22).

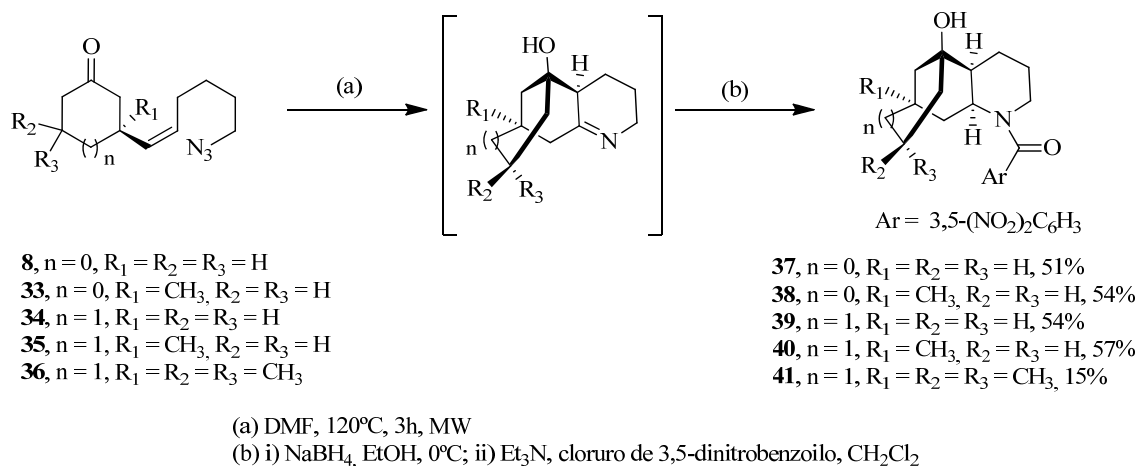


Esquema 2.22. Síntesis de los azido alquenos **33** a **36**.

El calentamiento de estos compuestos (**33-36**) durante 3 horas en DMF a 120°C en el reactor microondas condujo a los correspondientes imino alcoholes en todos los casos tal y como se observó en los espectros de ^1H -RMN de los crudos de reacción (Esquema 2.23). Sin embargo, los intentos de purificación de los mismos no permitieron aislarlos para poder llevar a cabo su caracterización. Esto se debe a la ya conocida facilidad de las piperideinas a oxidarse.²⁸ Se optó por tanto por la inmediata reducción con NaBH_4 y posterior acilación de las aminas con cloruro de 3,5-dinitrobenzoilo para sintetizar las amidas **38-41** que sí pudieron aislarse y

²⁸ La tendencia a la oxidación de las piperideinas 3-sustituidas ha sido observada y estudiada anteriormente: a) N. De Kimpe, M. Keppens, *Tetrahedron* **1996**, 52, 3705-3718; b) L. A. Cohen, B. Witkop, *J. Am. Chem. Soc.* **1955**, 77, 6595-6600.

caracterizarse sin problema. Así los rendimientos que se muestran son los de las tres etapas conjuntas: reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición de enamina, reducción de la imina y acilación. Además se llevó a cabo también la reducción y acilación del imino alcohol **10**, obtenido desde el azido alqueno **8**.



Esquema 2.23. Síntesis de las amidas **37** a **41**.

2.2.1.2.- Síntesis de imino alcoholes tetracíclicos.

Alentados por los buenos resultados en la obtención de estos imino alcoholes mediante reacción en cascada se pensó en la posibilidad de preparar sustratos más complejos mediante esta metodología. Aprovechando la existencia de dos carbonos nucleófilos en las iminas cíclicas se podría llevar a cabo una doble adición de enamina sobre enonas cíclicas: una adición 1,4 (adición tipo Michael), seguida de una adición 1,2 sobre la cetona.

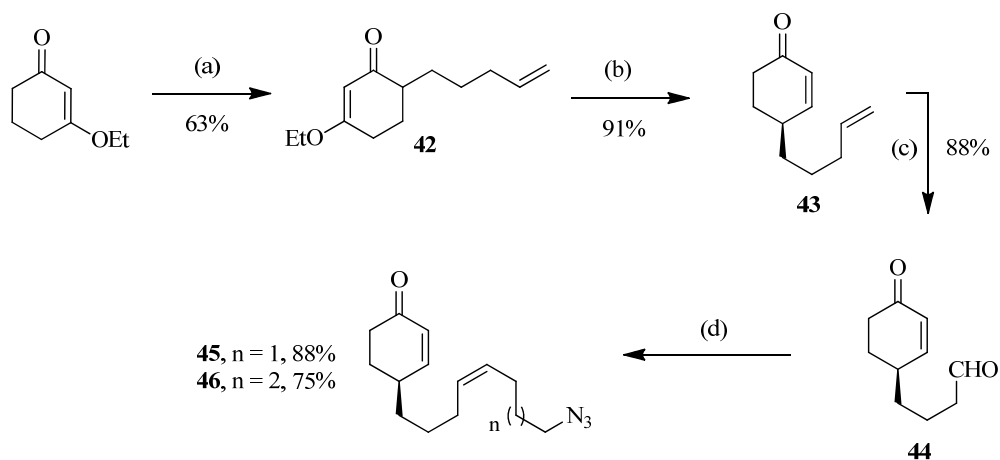
Con este objetivo se prepararon las azido dienonas **45** y **46** mediante alquilación de Stork-Danheiser²⁹ de la 3-etoxi-2-ciclohexen-1-ona con yoduro de 4-petenilo para dar el compuesto **43** (Esquema 2.24). A continuación se sometió dicho producto a ozonólisis en presencia de Sudan red 7B³⁰ como indicador³¹ para oxidar selectivamente el doble enlace terminal con lo que se obtuvo el aldehído **44**. Finalmente se emplearon las sales de fosfonio **4** y **6** como en los casos

²⁹ G. A. Stork, R. L. Danheiser, *J. Org. Chem.* **1973**, 38, 1775-1776.

³⁰ T. Veysoglu, L. A. Mitscher, J. K. Swayze, *Synthesis*, **1980**, 807-810.

³¹ Una vez oxidado el doble enlace terminal más reactivo, se va consumiendo el indicador con el ozono, apreciándose la desaparición del color rosa de la mezcla de reacción y evitando que se comience a oxidar el otro doble enlace de la molécula.

anteriores para funcionalizar la cadena con un grupo azida obteniendo así a los compuestos **45** y **46** deseados.



(a) LDA, yoduro de 4-pentenilo, THF, -78°C

(b) i) LiAlH_4 , THF/ Et_2O ; ii) HCl , THF

(c) i) O_3 , Sudan red 7B, CH_2Cl_2 , -78°C ; ii) PPh_3

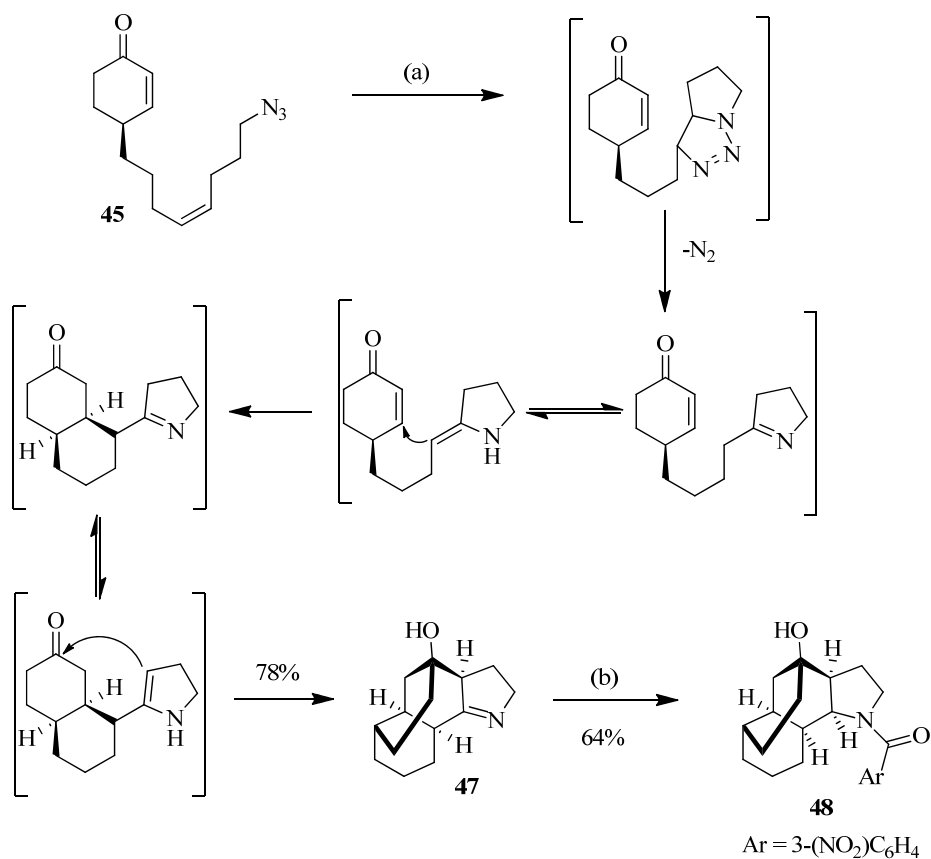
(d) sal de fosfonio **4**, KHMDS, THF, -78°C para **45**; sal de fosfonio **6**, KHMDS, THF/ CH_2Cl_2 (9:1), -78°C para **46**

Esquema 2.24. Síntesis de los azido alquenos **45** y **46**.

El calentamiento de una disolución del producto **45** con DBU en una mezcla de DMF/ EtOH (4:1) durante tres horas a 120°C en el reactor microondas condujo al imino alcohol tetracíclico **47** con un rendimiento del 78% y de manera totalmente diastereoselectiva (Esquema 2.25).³² La formación de este producto está mediada por una reacción de cicloadición 1,3-dipolar azida-alqueno intramolecular que conduce a la triazolina, descomposición de la misma y formación de la imina, adición 1,4 de la enamina exocíclica al doble enlace conjugado y adición 1,2 de la enamina endocíclica a la cetona. Así mediante esta triple reacción en cascada se generan tres nuevos ciclos y cuatro centros estereogénicos nuevos en un solo paso de reacción y con un total diastereocontrol. La posterior reducción de la imina con NaBH_4 en etanol y acilación de la amina con cloruro de 3-nitrobenzoilo en presencia de Et_3N , condujo finalmente a la amida **48**. Dicho producto permitió además obtener la confirmación de la configuración relativa del imino alcohol mediante un estudio de difracción de rayos X (Figura 2.2).³³

³² Se llevó a cabo también esta reacción sin emplear DBU ni etanol, únicamente calentando el compuesto **45** en DMF y el resultado fue la imina fruto de la cicloadición 1,3-dipolar, pero no tuvo lugar bajo esas condiciones la adición 1,4 ni 1,2 de la enamina.

³³ Los datos de difracción de rayos X del compuesto **48** se encuentran en el anexo II.



(a) DBU, DMF/EtOH (4:1), 120°C, MW, 3h

(b) i) NaBH₄, EtOH, 0°C; ii) cloruro de 3-nitrobenzoilo, Et₃N, CH₂Cl₂

Esquema 2.25. Síntesis del imino alcohol tetracíclico **47** y la amida **48**.

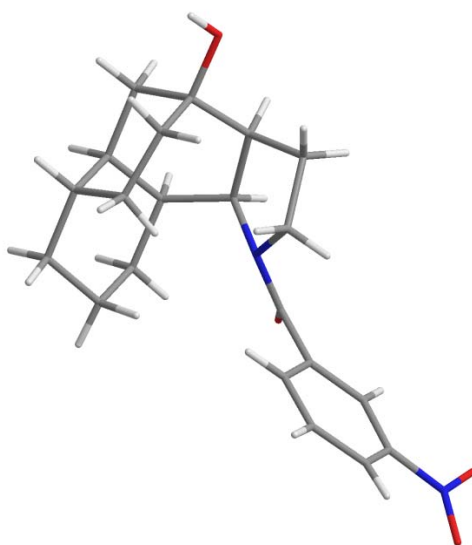
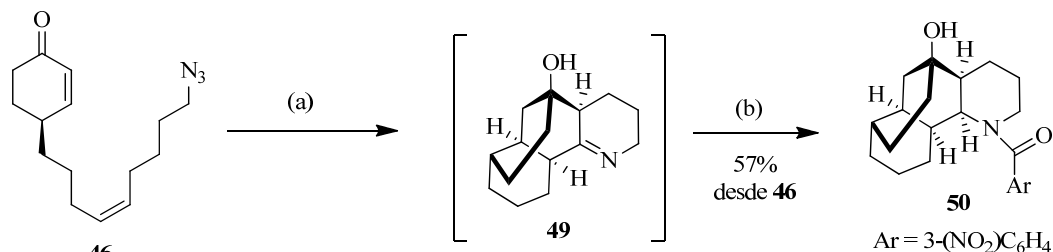


Figura 2.2. Estructura de rayos X del compuesto **48**.

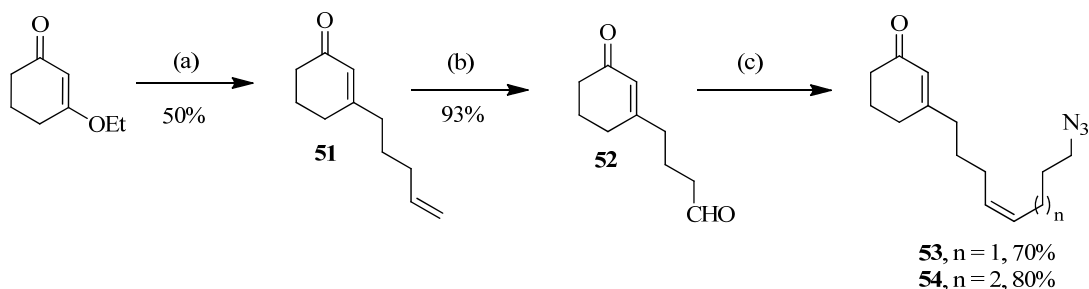
También se obtuvo muy buen resultado en la ciclación del compuesto **46** sin más que calentando tres horas en el reactor microondas a 120°C en DMF. De esta manera se formó el imino alcohol correspondiente **49** como un único diastereoisómero (Esquema 2.26). Sin embargo, debido a su inestabilidad y tendencia a la oxidación, fue transformado en la amida **50**³⁴ mediante reducción y acilación.



(a) DMF, 120°C, MW, 3h
(b) i) NaBH₄, EtOH, 0°C; ii) cloruro de 3-nitrobenzoilo, Et₃N, CH₂Cl₂

Esquema 2.26. Síntesis de la amida tetracíclica **50**.

A continuación se prepararon otras dos azido dienonas con las que tener acceso a imino alcoholes tetracíclicos. En este caso se sintetizaron ciclohexenonas 3-sustituidas a partir de la 3-etoxi-2-ciclohexen-1-ona (Esquema 2.27). Para ello, en primer lugar se llevó a cabo la adición del magnesiano derivado del 1-bromo-4-penteno con posterior hidrólisis ácida, lo que condujo al compuesto **51**.³⁵ Posteriormente, la ozonólisis del doble enlace terminal, de nuevo en presencia de Sudan Red 7B, permitió obtener el aldehído **52** con muy buen rendimiento. Finalmente se sintetizaron los azido alquenos **53** y **54** mediante reacciones de Wittig con las sales de fosfonio **4** y **6** respectivamente.



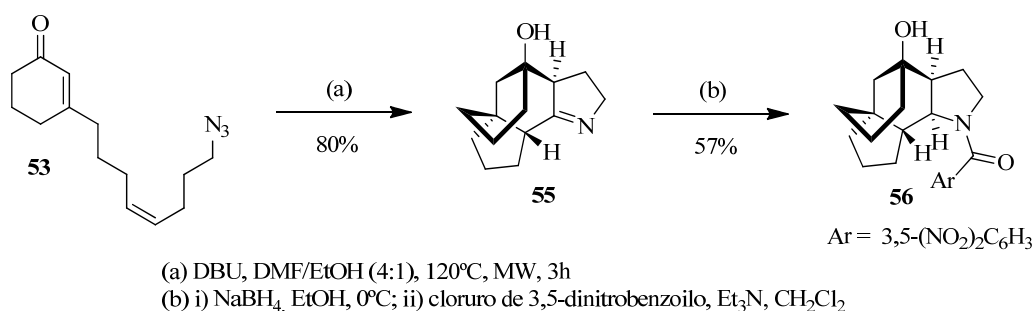
(a) i) Mg, 1-bromo-4-penteno, Et₂O, -78°C; ii) HCl
(b) i) O₃, Sudan red 7B, CH₂Cl₂, -78°C; ii) PPh₃
(c) sal de fosfonio **4**, KHMDS, THF, -78°C para **53**; sal de fosfonio **6**, KHMDS, THF/CH₂Cl₂ (9:1), -78°C para **54**

Esquema 2.27. Síntesis de los azido alquenos **53** y **54**.

³⁴ La estereoquímica del producto se asignó en base al espectro NOESY y por analogía con el compuesto **48** del cual se pudo determinar la estructura por difracción de rayos X.

³⁵ K. E. Harding, J. L. Cooper, P. M. Puckett, *J. Org. Chem.* **1979**, *44*, 2834-2838.

En primer lugar se cicló al azido alqueno **53** bajo las condiciones ya optimizadas y se obtuvo el imino alcohol espiránico **55** con un rendimiento del 80% y como un único diastereoisómero (Esquema 2.28).³⁶ De nuevo mediante esta triple reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición 1,4/adición 1,2 se están formando tres nuevos ciclos en una sola etapa y cuatro centros estereogénicos nuevos, dos de ellos además carbonos cuaternarios, de manera totalmente diastereoselectiva.



Esquema 2.28. Síntesis del imino alcohol tetracíclico **55** y la amida **56**.

También en este caso se pudo confirmar la estereoquímica relativa del producto gracias al estudio por difracción de rayos X de la amida **56**³⁷ que fue obtenida por reducción estereoselectiva de la imina y acilación con cloruro de 3,5-dinitrobenzoilo (Figura 2.3).

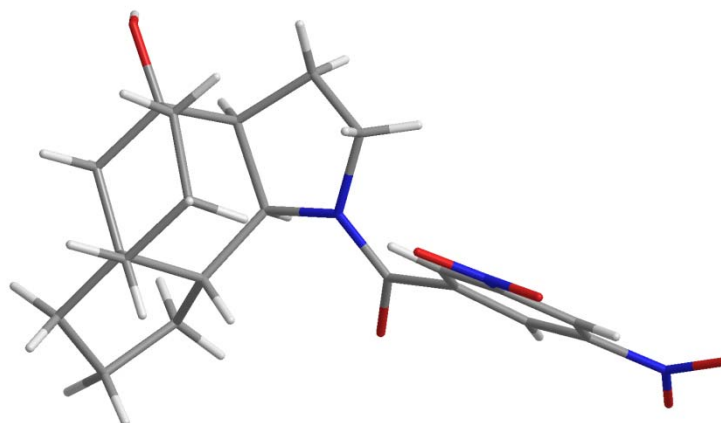
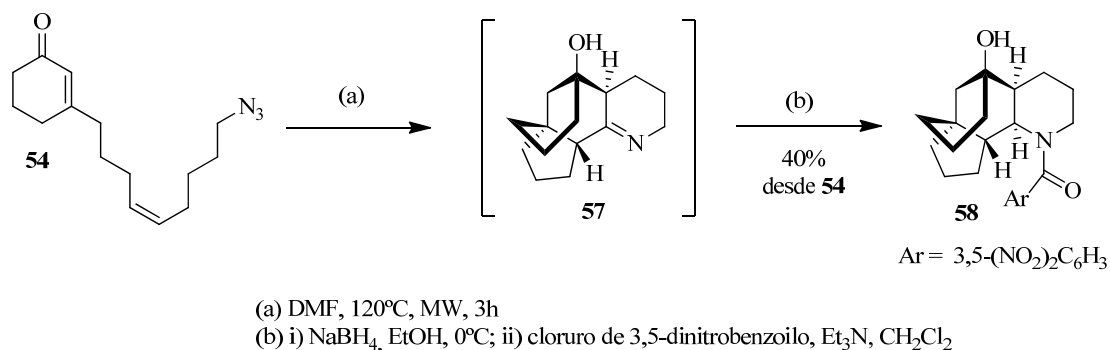


Figura 2.3. Estructura de rayos X del compuesto **56**.

³⁶ Al calentar el producto **53** únicamente en DMF se observó de nuevo que no tenían lugar las adiciones 1,4 ni 1,2.

³⁷ Los datos de difracción de rayos X del compuesto **56** se encuentran en el anexo II.

Igualmente se pudo obtener el imino alcohol tetracíclico **57** por reacción en cascada del azido alqueno **54** (Esquema 2.29). En este caso de nuevo la piperideina intermedia resultó demasiado inestable para poder ser aislada y caracterizada, por lo que se redujo para posteriormente acilar la amina. Así se obtuvo el producto **58** con un rendimiento del 40% (3 etapas).³⁸



Esquema 2.29. Síntesis de la amida **58**.

Es importante destacar de nuevo que en la síntesis de estos cuatro imino alcoholes tetracíclicos se está aumentando enormemente la complejidad estructural en una única etapa al crearse tres nuevos ciclos con un gran stereocontrol. Además, si bien la stereoquímica del producto final en el caso de los compuestos **47** y **49**, viene determinada por el centro stereoogénico creado en la etapa de alquilación de Stork-Danheiser; en el caso de los imino alcoholes **55** y **57**, los azido alquenos de partida **53** y **54** son aquirales lo cual abre las puertas a la aplicación de catalizadores quirales que pudiesen conducir a la obtención de los imino alcoholes de manera enantioméricamente pura.

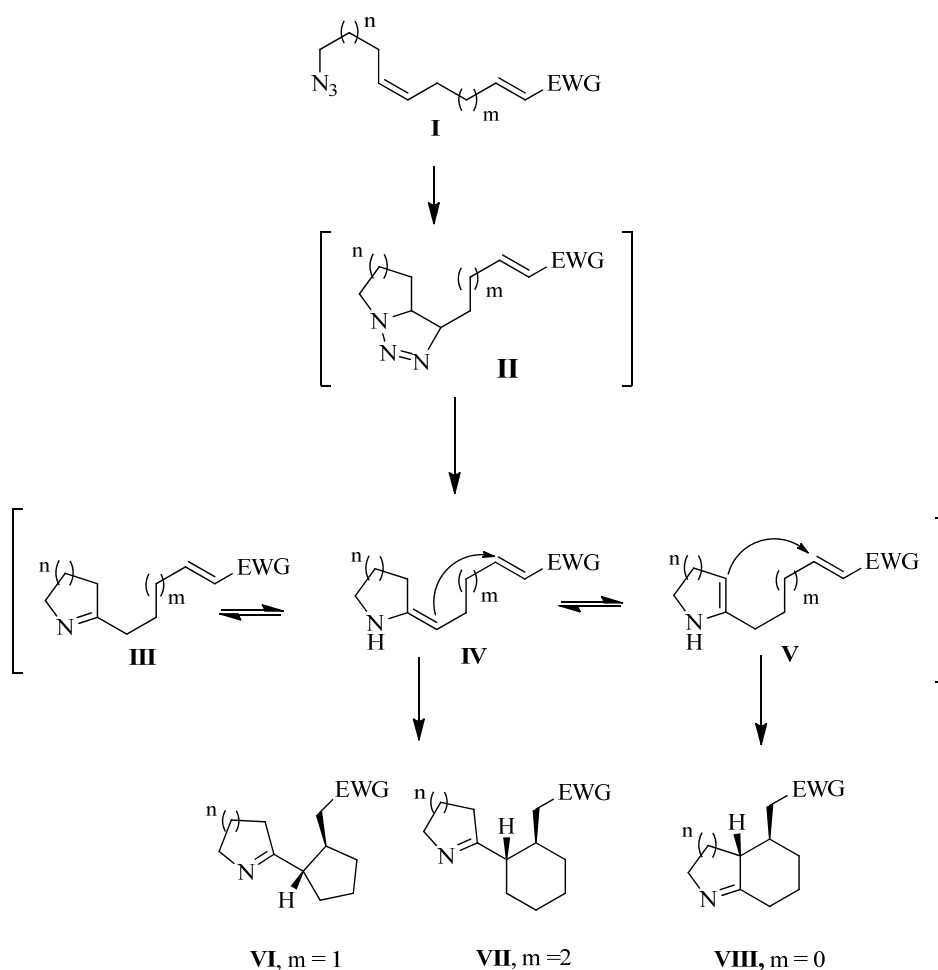
2.2.2.- Síntesis de iminas bicíclicas funcionalizadas mediante reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición de Michael.

La reacción de Michael³⁹ es uno de los métodos más comunes para la formación de nuevos enlaces C-C.¹⁷ Sin embargo, la adición de iminas cíclicas a aceptores de Michael ha sido muy poco estudiada como se comentó en la introducción de este capítulo^{11,12} y por ello se decidió explorar dicha reacción. La síntesis de los imino alcoholes tetracíclicos **47**, **49**, **55** y **57**

³⁸ La stereoquímica del producto se asignó de nuevo en base al espectro NOESY y por analogía con el compuesto **56** del cual se pudo confirmar la estructura por difracción de rayos X.

³⁹ A. J. Michael *Prakt. Chem.*, **1887**, 35, 349-356.

mediante reacción en cascada comentada anteriormente, constituye el primer ejemplo de adición intramolecular de una imina a un aceptor de Michael, en este caso una enona cíclica, que ha sido publicado.⁴⁰ Dados los buenos resultados obtenidos con estas cetonas cíclicas α,β -insaturadas se decidió seguir explorando esta reacción con otros sustratos. Nos planteamos la posibilidad de sintetizar azido alquenos lineales **I** que tras reacción de cicloadición 1,3-dipolar azida-alqueno intramolecular y descomposición de la triazolina formada **II**, diesen lugar a la correspondiente imina **III**, la cual en su forma tautomérica de enamina **IV** o **V** podría reaccionar con un aceptor de Michael para conducir a iminas bicíclicas funcionalizadas de diferente estructura según la longitud de la cadena carbonada (**VI**, **VII**, **VIII**) (Esquema 2.30).

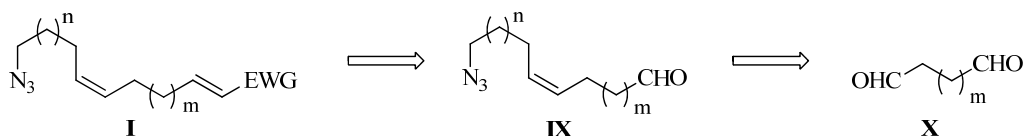


Esquema 2.30. Síntesis de iminas bicíclicas funcionalizadas.

La preparación de los azido alquenos lineales de partida con diferentes aceptores de Michael, estructuras tipo **I**, se planteó a partir de los dialdehídos **X** (Esquema 2.31). En primer lugar y mediante una reacción de Wittig con la sal de fosfonio funcionalizada con la azida, se

⁴⁰ I. de Miguel, B. Herradón, E. Mann, *Adv. Synth. Catal.* **2012**, 354, 1731-1736.

obtendrían los aldehídos **IX** para a continuación, formar el doble enlace electrón-deficiente empleando diferentes métodos según el aceptor de Michael a sintetizar. Así una vez preparados los aldehídos **IX**, éstos pueden ser empleados para formar diferentes azido alquenos.



Esquema 2.31. Retrosíntesis de los azido alquenos lineales.

2.2.2.1.- Síntesis de pirrolinas bicíclicas no fusionadas.

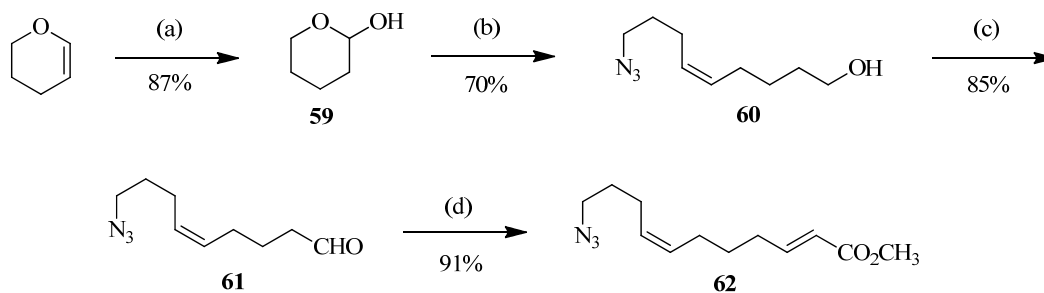
En primer lugar se decidió preparar las iminas bicíclicas no fusionadas de cinco miembros (Esquema 2.30, **VI** y **VII** con $n = 1$), dado que las pirrolinas han demostrado poseer mayor estabilidad que las piperideinas y por tanto su manipulación es más sencilla. Se escogió como compuesto modelo para el estudio de esta reacción en cascada el azido alqueno con un éster metílico α,β -insaturado y con una cadena de tres metilenos entre los dos dobles enlaces. Para la síntesis de este compuesto se partió del lactol **59** como equivalente sintético del dialdehído y cuya preparación es conocida a partir del 2,3-dihidropirano empleando HCl (Esquema 2.32).⁴¹ Sin necesidad de purificar este compuesto, se llevó a cabo a continuación la reacción de Wittig con la sal de fosonio **4** empleando KHMDs como base⁴² y THF como disolvente. Así se obtuvo el alcohol **60** con un rendimiento moderado del 47%. Para mejorar este rendimiento se probó la adición de CH_2Cl_2 como codisolvente,⁴³ ya que en otras ocasiones esto mejoraba la solubilidad de la sal de fosonio y nos había dado buen resultado. Se obtuvo así el correspondiente alcohol **60** con un 70% de rendimiento. La oxidación del alcohol primario empleando PCC condujo al correspondiente aldehído **61** con buen resultado.⁴⁴ Finalmente para formar el éster metílico α,β -insaturado se empleó el fosforano 2-(trifenilfosforaniliden)acetato de metilo en una reacción de Wittig. De esta manera se obtuvo el azido alqueno deseado **62** con muy buen rendimiento.

⁴¹ L. E. Schniepp, H. H. Geller, *J. Am. Chem. Soc.* **1946**, 68, 1646-1648; b) K. Kojima, M. Kimura, S. Ueda, Y. Tamaru, *Tetrahedron*, **2006**, 62, 7512-7520.

⁴² V. Ragoussis, S. Perdikaris, A. Karamolegkos, K. Magkios, *J. Agric. Food Chem.* **2008**, 56, 11929-11932.

⁴³ Ver parte experimental.

⁴⁴ E. J. Corey, J. W. Suggs, *Tetrahedron Lett.* **1975**, 16, 2647-2650.



- (a) HCl/H₂O
 (b) sal de fosfonio **4**, KHMDS, THF/CH₂Cl₂ (9:1), -78°C
 (c) PCC, CH₂Cl₂
 (d) Ph₃P=CHCO₂CH₃, CH₂Cl₂

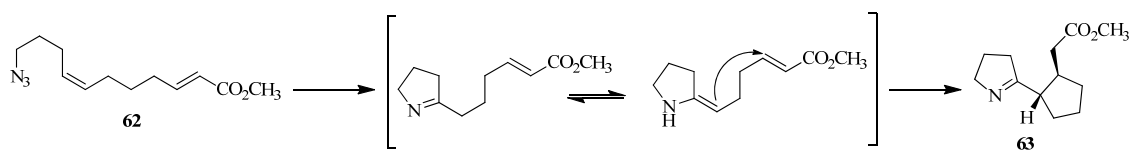
Esquema 2.32. Síntesis del compuesto **62**.

Con este producto se probaron diferentes disolventes y temperaturas para llevar a cabo la reacción de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición de Michael (Tabla 2.1). El resultado fue la formación de la esperada imina bicíclica **63** de manera totalmente diastereoselectiva,⁴⁵ excepto cuando se usó agua como disolvente (entrada 5), ya que en ese caso el azido alqueno se descompuso. Los rendimientos al emplear acetonitrilo o THF fueron sólo moderados (entradas 6 y 7). Mejores resultados se obtuvieron al llevar a cabo la reacción en metanol o tolueno (entradas 8 y 4), aunque con éste último fue necesario un mayor tiempo de reacción. Esto es debido a que la reacción es más lenta en disolventes apolares y a la menor constante dieléctrica del tolueno que hace que no absorba tan bien la radiación de microondas y por tanto la temperatura del medio de reacción no puede superar los 120°C.⁴⁶ También se obtuvieron buenos rendimientos empleando DMF, tanto a 120°C como a 140°C en el microondas (entradas 1 y 2), aunque con menos temperatura era necesario un mayor tiempo de reacción y no aumentaba el rendimiento. Igualmente se evaluó el empleo de un tubo sellado y baño de silicona como medio de calentamiento, pero fueron necesarias 16 horas para que la conversión fuera total y el rendimiento no fue mejor (entrada 3). Finalmente los mejores resultados se obtuvieron calentando en DMF a 140°C en el microondas durante 2 horas.

⁴⁵ La estereoquímica relativa de esta y otras iminas bicíclicas no fusionadas sintetizadas se asignó en base a los espectros bidimensionales NOESY en los que no se observó en ningún caso el pico de cruce entre los protones de los centros estereogénicos contiguos 1 y 2 del carbociclo.

⁴⁶ P. Lidström, J. Tierney, B. Wathey, J. Westman, *Tetrahedron*, **2001**, 57, 9225-9283.

Tabla 2.1. Optimización de la reacción en cascada.



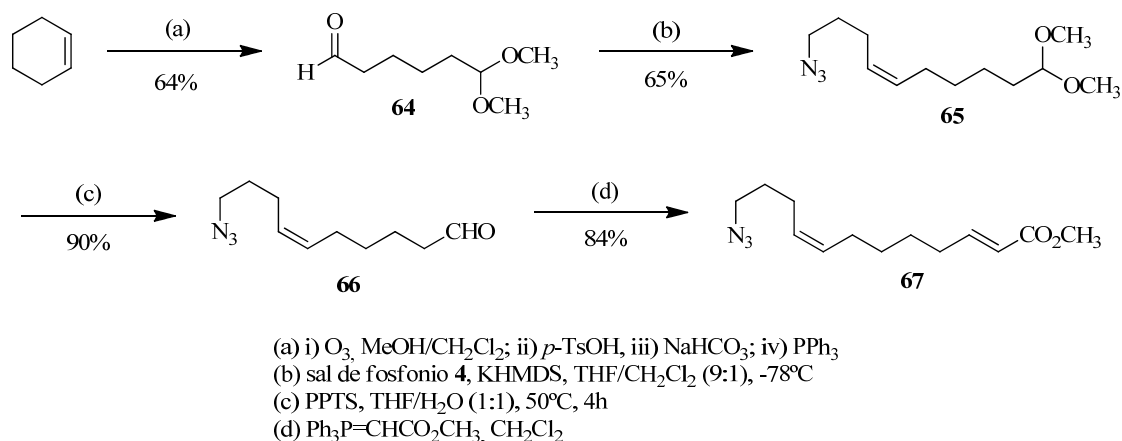
Entrada	Disolvente	Temperatura [°C]	Tiempo [h]	Rendimiento ^[a]
1	DMF	MW, 120°C	3	65 %
2	DMF	MW, 140°C	2	78 %
3	DMF	Tubo sellado, 120°C	16	68 %
4	Tolueno	MW, 120°C	4	70 %
5	H ₂ O	MW, 140°C	2	0 %
6	CH ₃ CN	MW, 140°C	3	56 %
7	THF	MW, 120°C	4	59 %
8	MeOH	MW, 140°C	2	67 %

[a] Rendimiento obtenido tras purificar en columna cromatográfica.

Una vez optimizadas las condiciones de reacción se decidió preparar otro éster metílico α,β -insaturado con un metileno más entre los dos dobles enlaces para sintetizar la pirrolina con el anillo de ciclohexilo. Dicho compuesto puede obtenerse mediante una estrategia de síntesis similar a la empleada en la preparación del azido alqueno **62**. Partiendo del ciclohexeno y mediante una ozonólisis en presencia de metanol y *p*-TsOH se obtuvo el 6,6-dimetoxihexenal **64** como producto mayoritario con un 64% de rendimiento (Esquema 2.33).⁴⁷ A continuación se realizó una reacción de Wittig y se llevó a cabo la desprotección del aldehído con *p*-toluensulfonato de piridinio (PPTS) en una mezcla de THF/H₂O obteniéndose el compuesto **66** con muy buen rendimiento.⁴⁸ Por último la reacción de este aldehído con el fosforano 2-(trifenilfosforaniliden)acetato de metilo permitió obtener el azido alqueno deseado **67**.

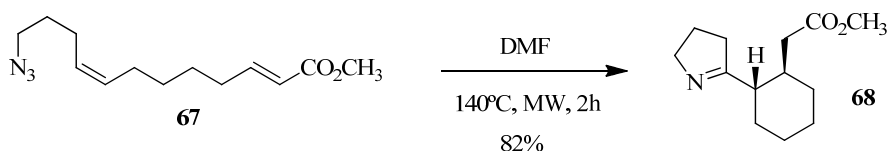
⁴⁷ a) R. E. Claus, S. L. Schreiber, *Organic Syntheses*, **1986**, 64, 150; b) R. E. Claus, S. L. Schreiber, *Organic Syntheses*, **1990**, 7, 168.

⁴⁸ S. E. Denmark, L. Gomez, *J. Org. Chem.* **2003**, 68, 8015-8024.



Esquema 2.33. Síntesis del compuesto **67**.

Al aplicar las condiciones de reacción anteriormente optimizadas para la reacción en cascada con este producto, se obtuvo la esperada imina bicíclica **68** (Esquema 2.34). El rendimiento fue similar al obtenido en la formación del producto con el anillo de ciclopentilo (**63**) y fue necesario el mismo tiempo de reacción. Se comprueba por tanto que en ambos casos se da la adición de la enamina exocíclica de manera rápida y limpia y se forman así en una sola etapa de reacción dos ciclos nuevos de manera totalmente diastereoselectiva obteniéndose las iminas de configuración *anti*.

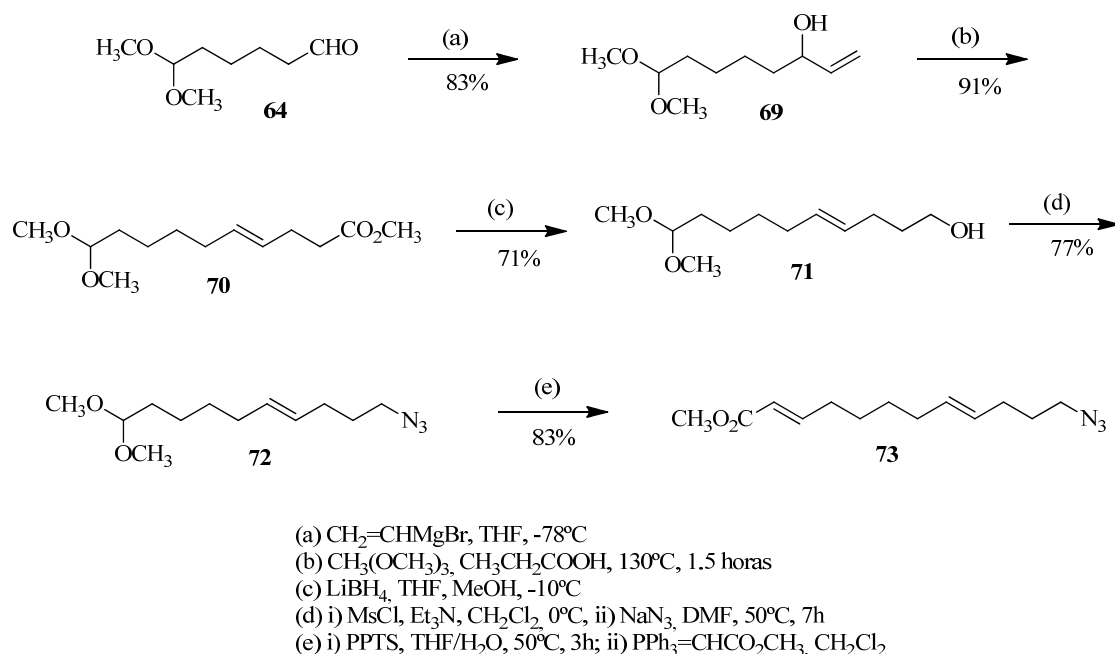


Esquema 2.34. Síntesis de la imina bicíclica **68**.

A continuación se estudió la influencia de la geometría del doble enlace inactivado en la reacción y estereoquímica del producto. Para ello fue preparado el compuesto **73** mediante una ruta de 5 etapas partiendo del producto **64** previamente sintetizado (Esquema 2.35). La adición de bromuro de vinilmagnesio sobre dicho aldehído condujo al alcohol alílico **69** con buen rendimiento. A continuación se llevó a cabo una transposición de Claisen-Johnson⁴⁹ empleando trimetilortoacetato y ácido propanoico para dar lugar al éster metílico **70** con el doble enlace de configuración *E*, el cual se trató con borohidruro de litio para obtener el alcohol **71**. Posteriormente y mediante formación del correspondiente mesilato y sustitución del mismo por el grupo azida empleando azida sódica se obtuvo el azido alqueno **72**. Finalmente se desprotegió

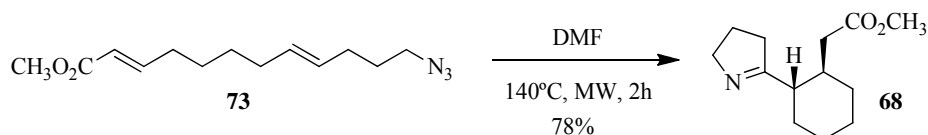
⁴⁹ W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-T. Li, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.* **1970**, 92, 741-743.

el aldehído con PPTS y se formó el éster metílico α,β -insaturado empleando el fosforano 2-(trifenilfosforaniliden)acetato de metilo.



Esquema 2.35. Síntesis del compuesto 73.

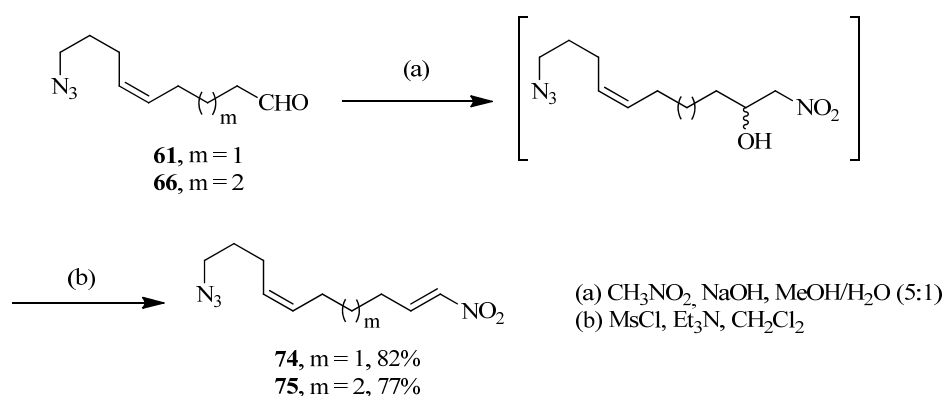
Al calentar una disolución del compuesto 73 en DMF durante 2 horas a 140°C en el microondas se comprobó que de nuevo se obtenía la misma imina bicíclica 68 de manera diastereoselectiva y con el mismo rendimiento (Esquema 2.36). Por lo tanto se puede concluir que ni la eficiencia de la reacción ni la estereoquímica del producto obtenido dependen de la geometría del doble enlace del azido alqueno. Es importante mencionar además que en ambos casos el único producto observado fue la imina, pero en ningún caso la aziridina.



Esquema 2.36. Ciclación del producto 73.

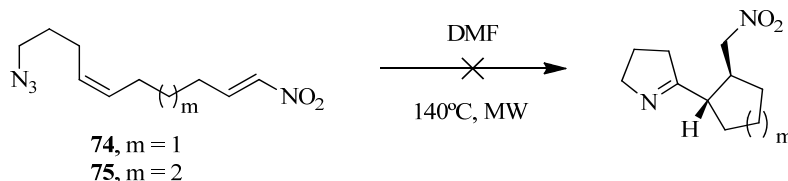
Comprobada la posibilidad de llevar a cabo la reacción con ésteres metílicos α,β -insaturados se pasó a explorar la generalidad de la reacción mediante el empleo de otros grupos electroatrayentes. Se optó en primer lugar por los grupos nitro α,β -insaturados ya que son muy

empleados como aceptores de Michael.⁵⁰ Además son muy útiles en química orgánica⁵¹ principalmente por la posibilidad de ser reducidos a aminas o transformarse en aldehídos o cetonas mediante la reacción de Nef.⁵² Por otro lado pueden sintetizarse fácilmente mediante la reacción de Henry⁵³ entre un aldehído o cetona y un nitro alcano y posterior eliminación del β-nitro alcohol. Así la reacción de los aldehídos **61** y **66**, anteriormente preparados, con nitrometano e hidróxido sódico en CH₃OH/H₂O (5:1),⁵⁴ y posterior formación y eliminación del mesilato de los alcoholes intermedios,⁵⁵ condujo a los productos **74** y **75** con un rendimiento del 82 y 77% respectivamente para las dos etapas (Esquema 2.37).



Esquema 2.37. Síntesis de los nitro alquenos **74** y **75**.

Al calentar una disolución del azido alqueno **74** en DMF a 140°C en el microondas se observó que la reacción era muy rápida y en tan sólo 30 minutos no quedaba producto de partida (Esquema 2.38). Sin embargo la reacción no era limpia como en el caso de los ésteres metílicos y al purificar el crudo sólo se obtuvieron trazas de la imina bicíclica deseada. Lo mismo ocurrió al llevar a cabo la reacción con el otro nitro alqueno **75** y no se pudo obtener el producto deseado.



Esquema 2.38. Ciclación de los nitro alquenos **74** y **75**.

⁵⁰ O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877-1894.

⁵¹ N. Ono en *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, **2001**.

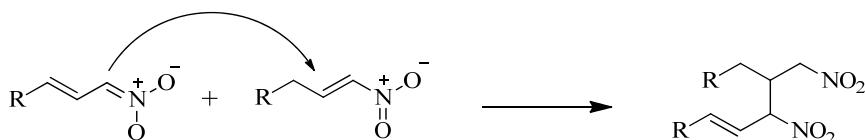
⁵² J. U. Neff, *Liebigs Ann. Chem.* **1894**, 280.

⁵³ a) L. C. R. Henry, *Acad. Sci. Ser. C.* **1895**, 120, 1265-1267 ; b) L. Henry, *Bull. Soc. Chim. Fr.* **1895**, 13, 999.

⁵⁴ B. M. Trost, C. Müller, *J. Am. Chem. Soc.* **2007**, 130, 2438-2439.

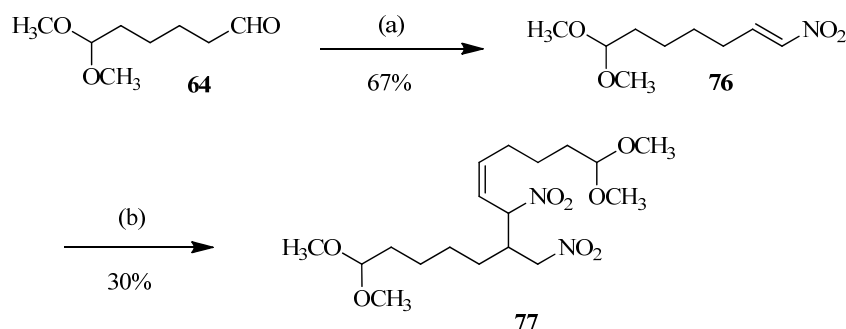
⁵⁵ D. Enders, C. Wang, J. W. Bats, *Angew. Chem. Int. Ed.* **2008**, 47, 7539-7542.

En un intento de averiguar por qué no se obtenían las iminas bicíclicas y qué otros procesos tenían lugar, se llevó a cabo un análisis del crudo de reacción por espectroscopía de masas. Éste mostró la formación de dímeros lo cual se debe a una reacción paralela descrita por el grupo de Anderson en la que se forma un nitronato que a su vez se adiciona a otra molécula de nitro alqueno para dar lugar a dímeros con dos grupos nitro (Esquema 2.39).⁵⁶



Esquema 2.39. Reacción de dimerización de nitro alquenos (Anderson, **2008**).⁵⁶

Para comprobar si realmente era esta reacción la que impedía la formación del producto deseado se preparó un nitro alqueno más sencillo (**76**) (Esquema 2.40). Efectivamente, al calentar este producto se observó la formación del dímero **77**. Con la intención de evitar este proceso se intentó llevar a cabo de nuevo la ciclación de los azido alquenos **74** y **75** a una menor temperatura con el propósito de ralentizar la dimerización, pero no se obtuvieron buenos resultados. Igualmente, dado que esta reacción no deseada es una reacción intermolecular y la reacción en cascada de formación de la imina es una reacción intramolecular, se llevó a cabo la reacción en condiciones más diluidas, pero no se pudo obtener el producto con mayor rendimiento. Un último intento de variar el disolvente empleando tolueno o metanol tampoco evitó la formación del dímero. Ante la imposibilidad de obtener el compuesto deseado funcionalizado con el grupo NO₂, se optó por sintetizar otro azido alqueno con un aceptor de Michael diferente que no diese lugar a este subproducto.

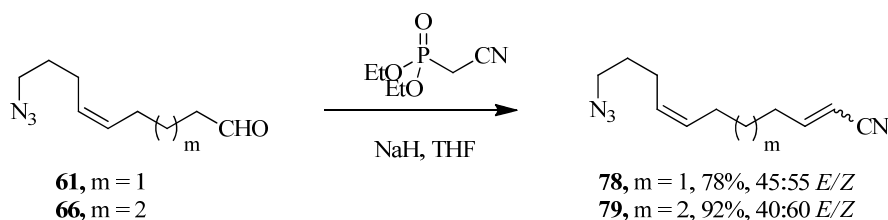


(a) i) CH₃NO₂, NaOH, MeOH/H₂O (5:1), ii) MsCl, Et₃N, CH₂Cl₂
(b) DMF, 80°C, 6h

Esquema 2.40. Síntesis y dimerización del nitro alqueno **76**.

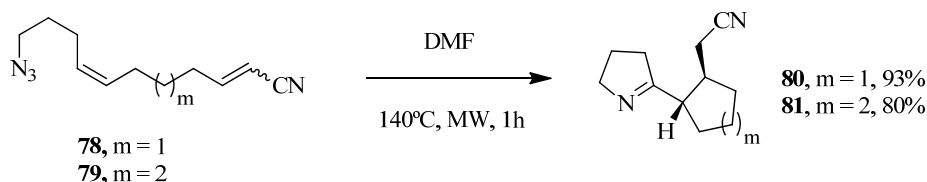
⁵⁶ J. C. Anderson, A. J. Blake, M. Mills, P. D. Ratcliffe, *Org. Lett.* **2008**, *10*, 4141-4143.

Se pensó en emplear un grupo ciano α,β -insaturado ya que la adición de una imina cíclica a este aceptor de Michael fue descrita anteriormente aunque de forma intermolecular¹¹ y por tanto podría ser un buen grupo electrófilo con el que llevar a cabo la reacción en cascada. Partiendo de nuevo de los aldehídos **61** y **66**, y mediante una reacción de Horner-Wardsworth-Emmons⁵⁷ empleando cianometilfosfonato de dietilo e hidruro sódico como base, se obtuvieron los compuestos **78** y **79** como una mezcla de isómeros *E/Z* en ambos casos (Esquema 2.41).



Esquema 2.41. Síntesis de los productos **78** y **79**.

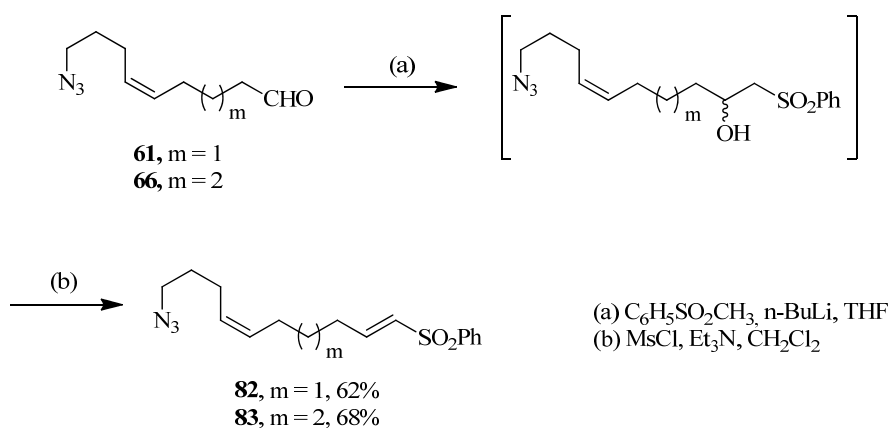
La separación de los isómeros *E/Z* mediante cromatografía en columna no resultó posible en ninguno de los dos casos y se procedió a calentar una disolución de la mezcla de ambos en DMF a 140°C en el microondas. En este caso sí se obtuvieron las correspondientes iminas bicyclicas funcionalizadas con el grupo ciano con muy buen rendimiento y de manera totalmente diastereoselectiva obteniéndose de nuevo las iminas con configuración relativa *anti* (Esquema 2.42). Es importante destacar que en este caso fue necesaria únicamente una hora de reacción, por lo que se puede deducir que el grupo ciano α,β -insaturado es más reactivo que el éster metílico y la adición de la enamina es más rápida. Además se observó el transcurso de la reacción y no se apreció diferencia de reactividad entre los isómeros *E* y *Z*. Igualmente al dar los dos isómeros un único producto se puede deducir que la geometría del doble enlace electrón-deficiente no influye en la stereoquímica de la imina final.



Esquema 2.42. Síntesis de las iminas bicyclicas **80** y **81**.

⁵⁷ a) L. Horner, H. M. R. Hoffmann, H. G. Wippel, *Ber.* **1958**, *91*, 61-63; b) L. Horner, H. M. R. Hoffmann, H. G. Wippel, G. Klahre, *Ber.* **1959**, *92*, 2499-2505; c) W. S. Wadsworth Jr., W. D. Emmons, *J. Am. Chem. Soc.* **1961**, *83*, 1733-1738; d) W. S. Wadsworth Jr. *Org. React.* **1977**, *25*, 73-253.

A continuación se pensó también en emplear como aceptor de Michael una vinil sulfona,⁵⁸ un grupo muy útil en química orgánica y fácil de preparar a partir de un aldehído mediante la adición del carbanión de una sulfona y posterior eliminación del alcohol. En nuestro caso elegimos la fenil metil sulfona de la cual se preparó el carbanión correspondiente con n-BuLi y se hizo reaccionar con los aldehído **61** y **66** respectivamente (Esquema 2.43). Los alcoholes así obtenidos se transformaron en los mesilatos correspondientes que directamente eliminaron en el medio de reacción⁵⁹ para formar las fenil sulfonas α,β -insaturadas **82** y **83** con un rendimiento del 62 y 68% respectivamente para las dos etapas.

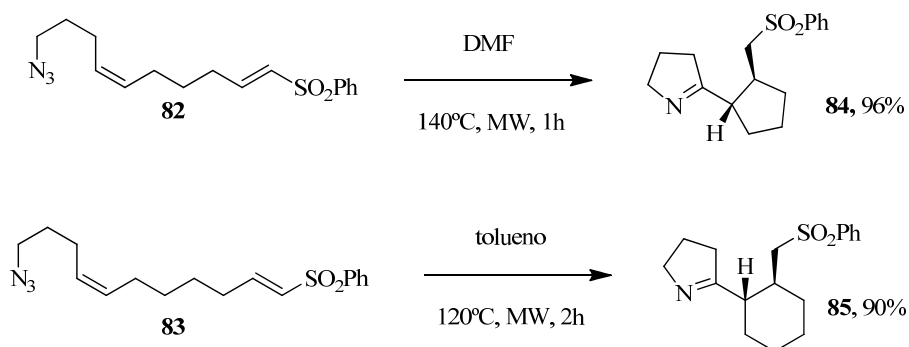


Esquema 2.43. Síntesis de las vinil sulfonas **82** y **83**.

De nuevo con este aceptor de Michael se probó la reacción en cascada en el microondas a 140°C en DMF. Así se obtuvo la imina bicíclica con el anillo de ciclopentilo **84** como un único diastereoisómero y con muy buen rendimiento en tan sólo una hora (Esquema 2.44). Sin embargo, al calentar una disolución del azido alqueno **83** en DMF se observó la formación de más subproductos y el rendimiento fue sólo moderado. Se pensó entonces en emplear tolueno como disolvente dado que también dio buenos resultados con el éster metílico. Así tras dos horas de reacción en el microondas a 120°C en tolueno se comprobó que la reacción era mucho más limpia que con DMF, obteniéndose la imina **85** con un 90% de rendimiento.

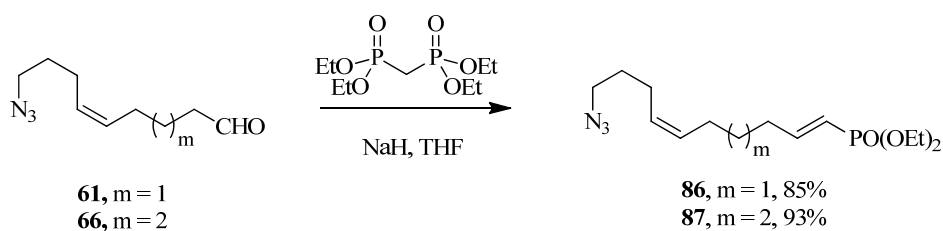
⁵⁸ Para una revisión sobre la preparación y reactividad de las vinil sulfonas ver: N. S. Simpkins, *Tetrahedron*, **1990**, *46*, 6951-6984.

⁵⁹ J. Adrio, M. Rodríguez Rivero, J. C. Carretero, *Org. Lett.* **2005**, *7*, 431-434.



Esquema 2.44. Síntesis de las iminas bicyclicas **84** y **85**.

Otro grupo aceptor de Michael interesante son los vinil fosfonatos. Los compuestos organofosforados son muy empleados en química⁶⁰ y poseen propiedades que les hacen muy útiles en diversos campos como química médica⁶¹ o materiales.⁶² La adición de Michael sobre vinil fosfonatos es ampliamente conocida,⁶³ aunque se ha limitado prácticamente al empleo de vinil fosfonatos con un grupo electrón-atrayente en posición α como un carbonilo o nitrilo, al aumentar así la reactividad y facilitar la adición del nucleófilo. En nuestro caso nos propusimos preparar azido alquenos con un grupo dietil fosfonato como aceptor de Michael para ver si era posible la adición de la enamina. Dicho grupo funcional se introdujo en la cadena por reacción de los aldehídos **61** y **66** con el metilendifosfonato de tetraetilo⁶⁴ mediante una reacción de Horner-Wardsworth-Emmons obteniéndose los productos **86** y **87** con muy buenos rendimientos en ambos casos (Esquema 2.45).



Esquema 2.45. Síntesis de los vinil fosfonatos **86** y **87**.

Al calentar una disolución del compuesto **86** en DMF a 140°C en el microondas durante dos horas, se observó que la reacción de cicloadición 1,3-dipolar azida-alqueno había sido completa, pero la adición de Michael era muy lenta, debido a la menor reactividad de los vinil

⁶⁰ N. Bricklebank en *Organophosphorus Chemistry*, Ed. D. W. Allen, J. C. Tebby, **2001**.

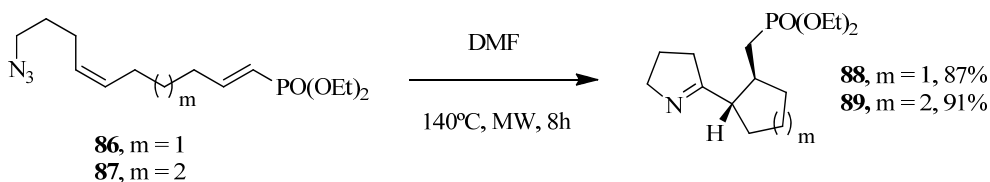
⁶¹ J. P. Krise, V. J. Stella, *Adv. Drug Delivery Rev.* **1996**, *19*, 287-310.

⁶² T. Baumgartner, R. Réau, *Chem. Rev.* **2006**, *106*, 4681-4727.

⁶³ T. Janecki, J. Kedzia, T. Wasek, *Synthesis*, **2009**, 1227-1254.

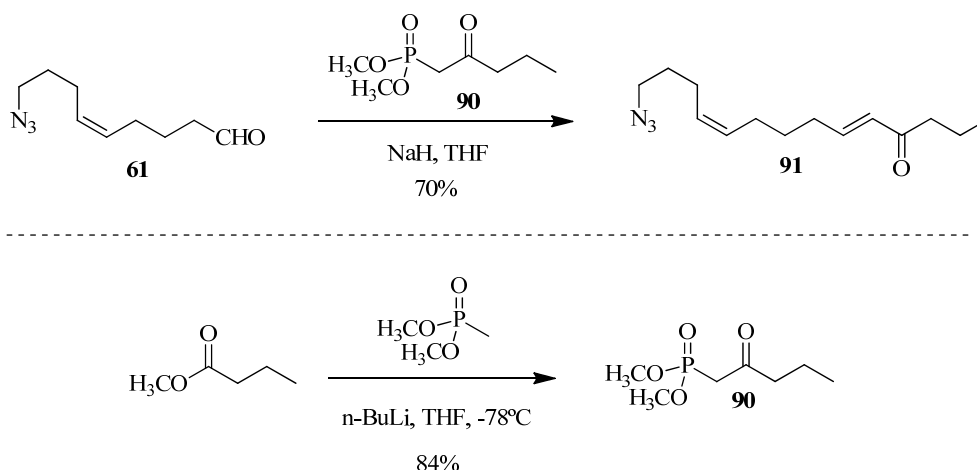
⁶⁴ R. J. Cox, J. S. Gibson, A. T. Hadfield, *ChemBioChem*. **2005**, *6*, 2255-2260.

fosfonatos comparada con otros aceptores de Michael. Finalmente fueron necesarias 8 horas de reacción en el microondas para obtener el producto de adición, si bien este mayor tiempo de reacción no afectó al rendimiento ya que se obtuvo la imina bicíclica **88** con un 87% de rendimiento y como un único diastereoisómero (Esquema 2.46). Lo mismo ocurrió con el azido alqueno **87**, con el que también fue necesario un tiempo de reacción de 8 horas en el microondas para obtener el producto deseado **89** con muy buen rendimiento.



Esquema 2.46. Síntesis de las iminas bicíclicas **88** y **89**.

Finalmente se pensó en emplear cetonas α,β -insaturadas como aceptor de Michael. En la síntesis de los imino alcoholes ya se llevó a cabo con éxito la adición de iminas a enonas cíclicas, pero en este caso se planteó la adición a enonas lineales, una reacción que Movassaghi intentó llevar a cabo hace unos años aunque sin éxito.¹² Para estudiar esta reacción se sintetizó como modelo el azido alqueno **91** mediante una reacción de Horner-Wardsworth-Emmons empleando el aldehído **61** y el fosfonato **90**⁶⁵ sintetizado a partir de metilfosfonato de dimetilo y butirato de metilo (Esquema 2.47).⁶⁶

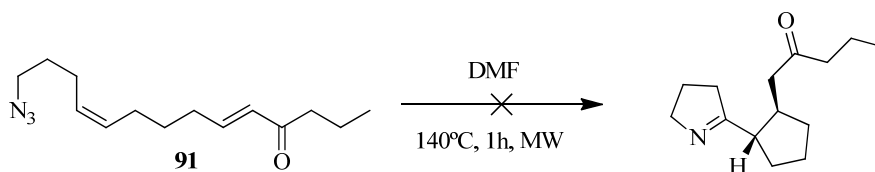


Esquema 2.47. Síntesis del fosfonato **90** y del compuesto **91**.

⁶⁵ K. J. Frankowski, B. Neuenswander, J. Aubé, *J. Comb. Chem.* **2008**, *10*, 721-725.

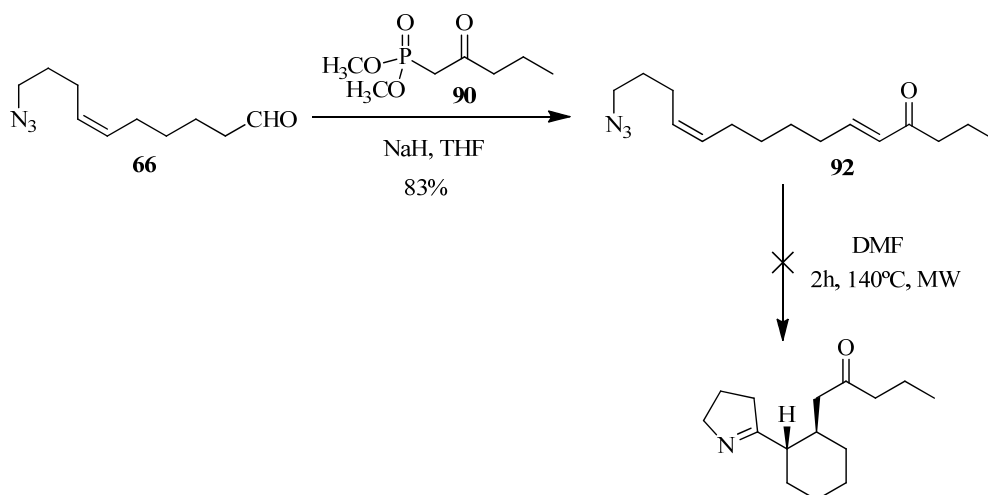
⁶⁶ N. A. Khatri, H. F. Schmitthenner, J. Shringarpure, S. M. Weinreb, *J. Am. Chem. Soc.* **1981**, *103*, 6387-6393.

Al calentar una disolución del producto **91** en DMF a 140°C en el reactor microondas durante una hora, se obtuvo un complejo crudo de reacción con varios compuestos (Esquema 2.48). Se probó también la reacción en tolueno, pero el resultado no fue mejor. Para intentar identificar los productos y estudiar cuál o cuáles eran los procesos que estaban teniendo lugar, se intentó purificar por columna cromatográfica con gel de sílice, pero no se pudo obtener ninguna muestra pura para identificar los compuestos. Se probó también con otras fases estacionarias como alúmina neutra y sílica gel desactivada, pero tampoco se pudieron purificar los productos formados en la reacción de microondas para su caracterización debido probablemente a su descomposición.



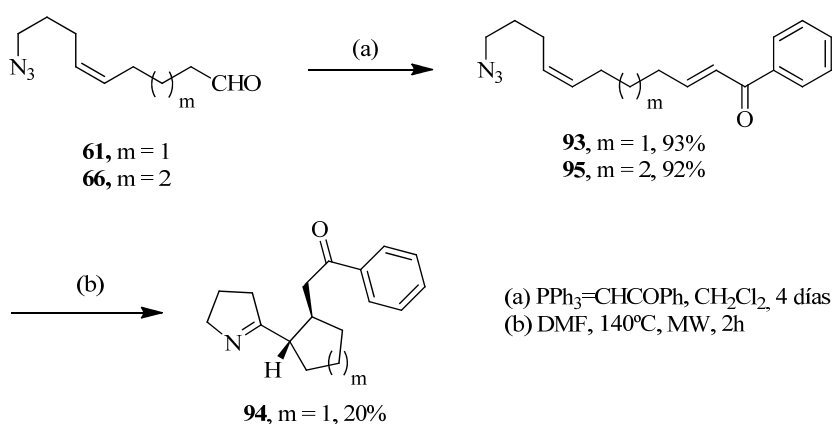
Esquema 2.48. Ciclación de la azido dienona **91**.

Se preparó entonces la enona **92** para ver si en ese caso era posible la formación y purificación de la correspondiente imina (Esquema 2.49). Sin embargo, de nuevo al calentar el producto en DMF bajo radiación de microondas se obtuvo una compleja mezcla de productos que descompusieron en la columna cromatográfica y de la cual tampoco se pudo aislar la imina bicíclica deseada.



Esquema 2.49. Síntesis y ciclación de la enona **92**.

A continuación se sintetizaron los azido alquenos con una fenil enona como electrófilo, para ver si se podían obtener mejores resultados. Dichos productos se prepararon a partir de los aldehídos **61** y **66** por reacción con 1-fenil-2-(trifenilfosforaniliden)etanona en diclorometano a temperatura ambiente durante cuatro días (Esquema 2.50). En este caso al calentar una disolución del azido alqueno **93** en DMF durante 2 horas en el microondas a 140°C, se observó la formación de la imina bicíclica **94** en el crudo de reacción, aunque al purificar sólo se obtuvo un rendimiento del 20% debido a su parcial descomposición. Igualmente se intentó llevar a cabo la reacción en cascada con el compuesto **95** en las mismas condiciones, pero no se obtuvo la imina bicíclica esperada, sino un complejo crudo de reacción en el que no se pudieron identificar los productos formados al intentar purificar mediante cromatografía en columna.



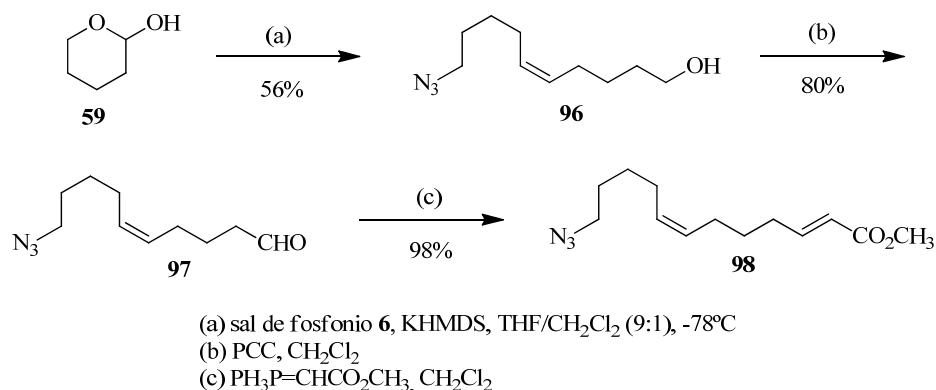
Esquema 2.50. Síntesis y ciclación de las fenil enonas **93** y **95**.

Dados los malos resultados obtenidos con las cetonas α,β -insaturadas y la imposibilidad de purificar los productos obtenidos, se abandonó el empleo de este grupo atractor de electrones y se decidió estudiar la formación de las piperideinas análogas con los aceptores de Michael que sí dan buenos resultados (CO_2CH_3 , CN, SO_2Ph , $\text{PO}(\text{OEt})_2$).

2.2.2.2.- Síntesis de piperideinas bicíclicas no fusionadas.

A pesar de la ya conocida y comprobada inestabilidad de la iminas cíclicas de seis miembros²⁶ se decidió estudiar la síntesis de las piperideinas no fusionadas a partir de los correspondientes azido alquenos. En primer lugar se preparó un azido alqueno con un éster metílico como grupo electroatrayente con la intención de optimizar las condiciones de reacción necesarias para obtener la correspondiente imina bicíclica como se hizo para la síntesis de las

pirrolinas. Partiendo de nuevo del lactol **59** y mediante reacción de Wittig con la sal de fosfonio **6** se formó el alcohol **96** (Esquema 2.51). En este caso de nuevo fue necesaria la adición de CH_2Cl_2 como codisolvente para mejorar la solubilidad de la sal de fosfonio. La oxidación del alcohol se llevó a cabo con PCC para obtener el correspondiente aldehído con buen rendimiento. Por último se empleó 2-(trifenilfosforaniliden)acetato de metilo para sintetizar el azido alqueno deseado **98** con un excelente rendimiento.

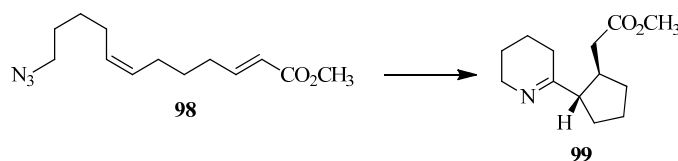


Esquema 2.51. Síntesis del compuesto **98**.

Para llevar a cabo la reacción en cascada se ensayaron varias condiciones (Tabla 2.2). Se probó en primer lugar con DMF a 140°C en el microondas, las condiciones empleadas para la síntesis de las pirrolinas, y efectivamente se obtuvo la esperada imina bicíclica **99** de manera diastereoselectiva, pero con un rendimiento moderado (entrada 1). Para intentar mejorar este resultado se probó con metanol como disolvente, pero el rendimiento fue similar (entrada 4). Con tolueno fue necesaria una hora más de reacción y el rendimiento fue algo más bajo (entrada 2). Finalmente se comprobó que la mezcla de DMF con etanol en proporción 4:1, si bien no conseguía aumentar la cantidad de imina obtenida, sí permitía acelerar un poco la reacción (entrada 3) y se escogieron estas condiciones como las óptimas para la síntesis de estas piperideinas.⁶⁷

⁶⁷ En ningún caso se observó la formación de la correspondiente aziridina.

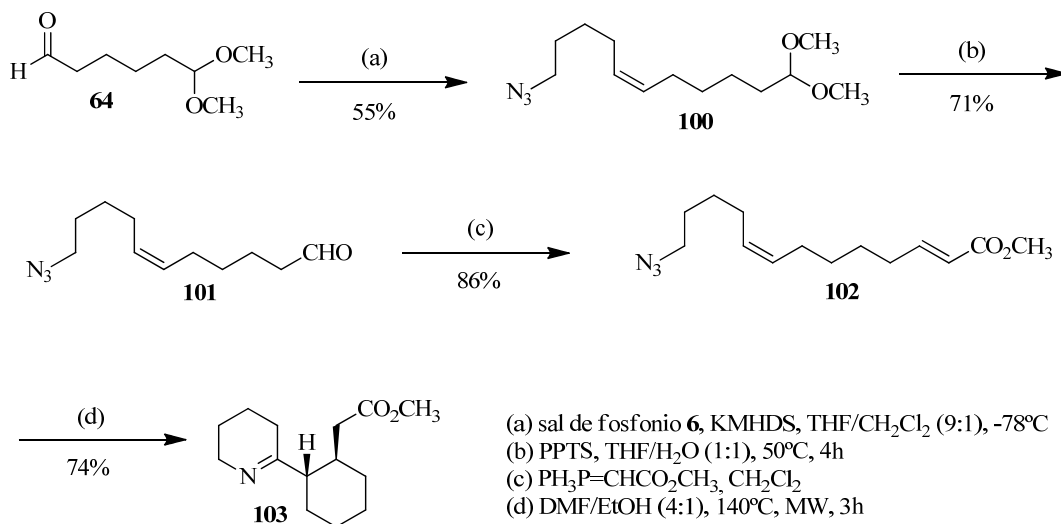
Tabla 2.2. Optimización de la reacción en cascada.



Entrada	Disolvente	Temperatura [°C]	Tiempo [h]	Rendimiento [%] ^[a]
1	DMF	MW, 140°C	3	59
2	Tolueno	MW, 120°C	4	52
3	DMF/EtOH (4:1)	MW, 140°C	2	63
4	MeOH	MW, 140°C	3	60

[a] Rendimiento obtenido tras purificar en columna cromatográfica.

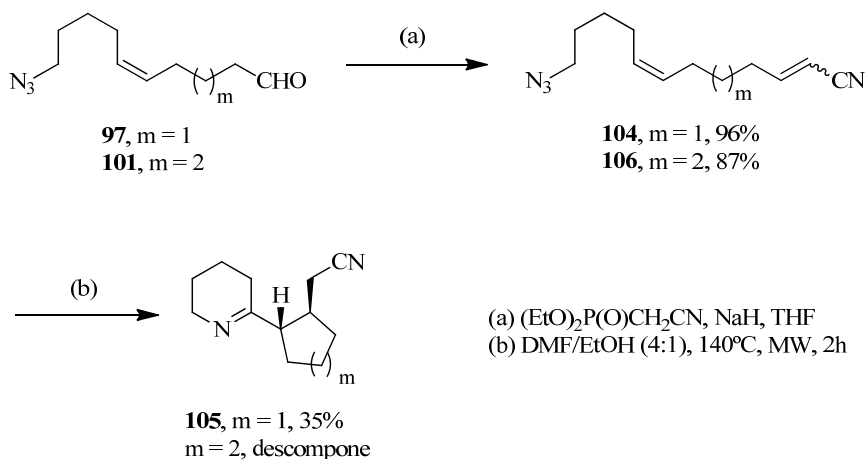
El éster metílico α,β -insaturado **102** también se preparó de manera sencilla partiendo del 6,6-dimetoxihexenal (**64**) por reacción de Wittig, desprotección del aldehído con PPTS y reacción con el mismo fosforano (Esquema 2.52). A continuación se aplicaron las condiciones anteriormente optimizadas y se obtuvo la imina bicíclica **103** con un rendimiento similar, aunque fue necesaria una hora más que con el azido alqueno **98** para que la conversión fuera completa.



Esquema 2.52. Síntesis y ciclación del azido alqueno **102**.

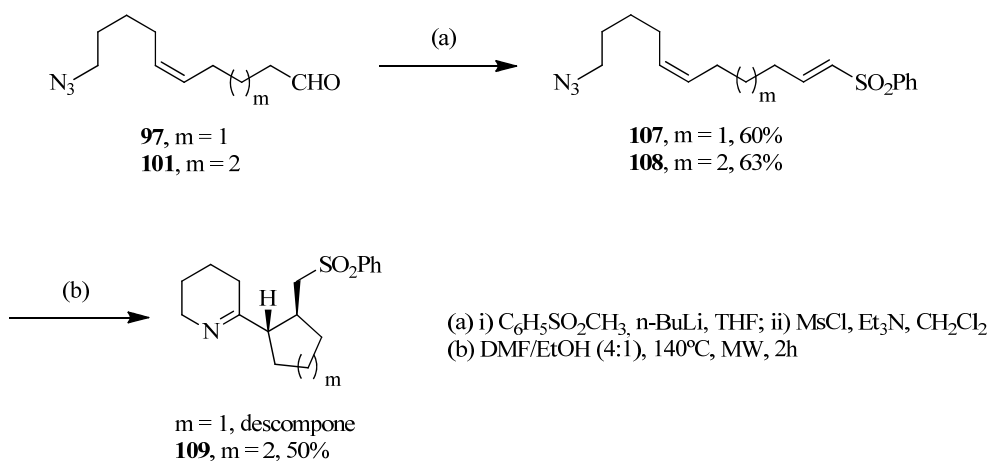
Se prepararon también los azido alquenos con el grupo ciano α,β -insaturado como aceptor de Michael dado el buen resultado obtenido con las pirrolinas y este grupo electroatrayente. Para ello se hizo reaccionar a los aldehídos **97** y **101** con cianometilfosfonato de dietilo y se obtuvieron los compuestos **104** y **106** respectivamente como una mezcla de isómeros *E/Z* que

no pudieron separarse (Esquema 2.53). El calentamiento de una disolución del producto **104** en DMF/EtOH (4:1) durante 2 horas en el microondas a 140°C condujo a la imina bicíclica **105**. Sin embargo, al llevar a cabo su purificación mediante columna cromatográfica sólo se recuperó el producto con un 35% de rendimiento. A su vez, al calentar el azido alqueno **106** en las mismas condiciones se observó la formación del producto esperado en el crudo de reacción, pero no fue posible caracterizar dicha imina debido a su descomposición en todos los intentos de purificación.



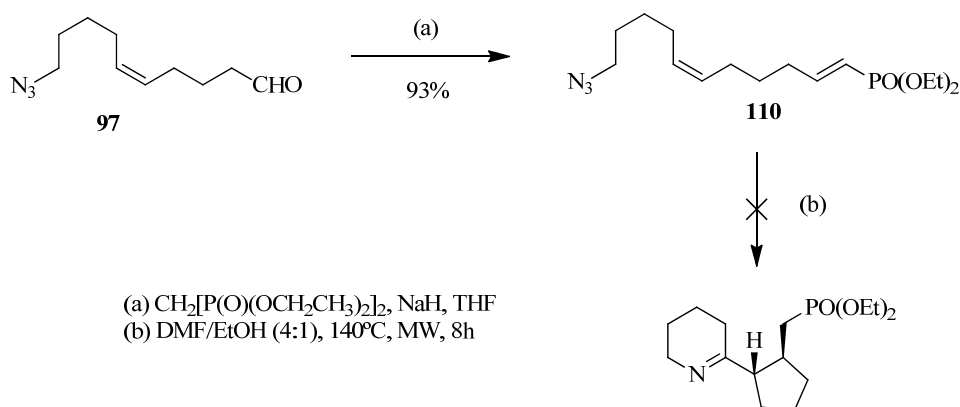
Esquema 2.53. Síntesis y ciclación de los azido alquenos **104** y **106**.

A continuación se sintetizaron los azido alquenos con una fenil sulfona α,β -insaturada mediante la reacción de los aldehídos **97** y **101** con fenil metil sulfona y n-BuLi en THF e inmediata eliminación de los alcoholes resultantes por transformación en los correspondientes mesilatos (Esquema 2.54). Así se obtuvieron los productos **107** y **108** con rendimientos del 60 y 63% respectivamente para las dos etapas. De nuevo se intentó llevar a cabo la reacción en cascada para la formación de la iminas bicíclicas en las condiciones optimizadas anteriormente. En ambos casos se observó la formación de estos productos deseados en los crudos de reacción, pero de ambos sólo se consiguió purificar el producto con el anillo de ciclohexilo (**109**) con un rendimiento del 50% mientras que la otra imina bicíclica con el anillo de ciclopentilo descompuso en la columna y no pudo aislarse a pesar de los numerosos intentos.



Esquema 2.54. Síntesis y ciclación de los azido alquenos **107** y **108**.

Por último se preparó el vinil fosfonato **110** empleando metilendifosfonato de tetraetilo a partir del aldehído **97** (Esquema 2.55). En este caso al calentar dicho producto en una mezcla de DMF/EtOH (4:1) a 140°C en el microondas se observó que la adición era de nuevo muy lenta debido a la menor reactividad de este aceptor de Michael. Sin embargo tiempos de reacción más largos no dieron como resultado la esperada imina bicíclica, sino la descomposición del producto, imposibilitando por tanto la síntesis de las piperideinas funcionalizadas con el grupo fosfonato de dietilo.



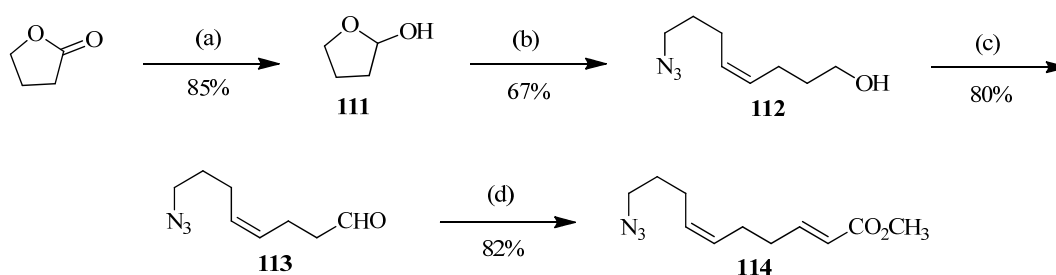
Esquema 2.55. Síntesis y ciclación del azido alqueno **110**.

Se puede concluir por tanto que las piperideinas, como ya era conocido, son muchos más sensibles y descomponen con mucha mayor facilidad que las pirrolinas. Esto hace que algunos de los productos no puedan llegar a purificarse y los que sí, únicamente se pueden obtener con moderados rendimientos.

2.2.2.3.- Síntesis de pirrolinas con estructura tipo 3,3a,4,5,6,7-hexahidro-2H-indol.

Las iminas cíclicas están en equilibrio con dos enaminas, exocíclica y endocíclica. Hasta ahora se ha estudiado la adición de la enamina exocíclica a diferentes aceptores de Michael para dar lugar a iminas bicíclicas no fusionadas. Sin embargo, nos planteamos también la posibilidad de llevar a cabo la adición de las enaminas endocíclicas para dar lugar a iminas bicíclicas fusionadas (estructuras tipo **VIII**, Esquema 2.30).

De nuevo se comenzó a estudiar la reacción en cascada para la preparación de pirrolinas que no presentan problemas de estabilidad y se escogió como modelo el azido alqueno con un éster metílico α,β -insaturado como aceptor de Michael. Este producto se pudo preparar a través de una ruta sencilla desde la γ -butirolactona (Esquema 2.56). La reducción de la misma con DIBAL condujo al lactol **111**.⁶⁸ A continuación se hizo reaccionar dicho compuesto con la sal de fosfonio **4** para obtener el alcohol **112**. La oxidación al aldehído **113** se llevó a cabo empleando PCC y por último una reacción de Horner-Wardsworth-Emmons con 2-(trifenilfosforaniliden)acetato de metilo permitió, como en ocasiones anteriores, obtener el azido alqueno **114** con buen rendimiento.



- (a) DIBAL, CH_2Cl_2 , -78°C
 (b) sal de fosfonio **4** KHMDS, THF/ CH_2Cl_2 (9:1), -78°C
 (c) PCC, CH_2Cl_2
 (d) $\text{PH}_3\text{P}=\text{CHCO}_2\text{CH}_3$, CH_2Cl_2

Esquema 2.56. Síntesis del compuesto **114**.

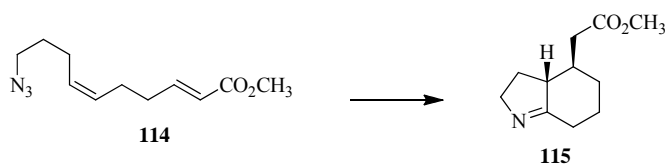
Una vez preparado este compuesto se comenzó la optimización de la reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición de enamina para la formación de la imina bicíclica **115** (Tabla 2.3). En primer lugar se empleó DMF como disolvente a 140°C en el MW y se obtuvo la correspondiente imina como un único diastereoisómero⁶⁹ y con un rendimiento del 55% (entrada 1). Un resultado similar se obtuvo con etanol (entrada 5). Sin

⁶⁸ A. W. Schammel, B. W. Boal, L. Zu, T. Mesganaw, N. K. Garg, *Tetrahedron*, **2010**, 66, 4687-4695.

⁶⁹ La estereoquímica de esta y otras iminas fusionadas se asignó en base a los espectros bidimensionales NOESY en los que no se observó en ningún caso el pico de cruce entre los protones de los dos centros estereogénicos formados.

embargo, al emplear tolueno únicamente tuvo lugar la cicloadición, pero no la adición de la enamina endocíclica a pesar de dejar la reacción varias horas a 120°C (entrada 2). Sí que se observó la formación de la imina bicíclica al llevar a cabo la reacción en una mezcla de tolueno y etanol aunque el rendimiento no superó el 30% (entrada 3). Finalmente el mejor resultado se obtuvo empleando metanol como disolvente a 140°C en el microondas, recuperándose la imina deseada con un 68% de rendimiento tras dos horas de reacción (entrada 4). Es importante destacar que en esta ocasión, salvo al emplear tolueno, no es necesaria ninguna base para que tenga lugar la adición de la enamina endocíclica de la pirrolina como ocurría en la síntesis de los imino alcoholes. Una vez optimizadas las condiciones de reacción para la obtención de estas iminas se pasó a preparar azido alquenos con otros aceptores de Michael.

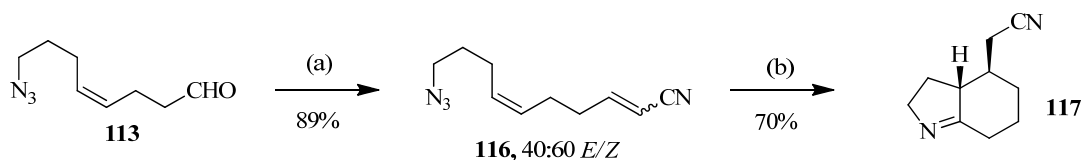
Tabla 2.3. Optimización de la reacción en cascada.



Entrada	Disolvente	Temperatura [°C]	Tiempo [h]	Rendimiento [%] ^[a]
1	DMF	MW, 140°C	2	55%
2	Tolueno	MW, 120°C	4	0%
3	Tolueno/EtOH (4:1)	MW, 120°C	4	30%
4	MeOH	MW, 140°C	2	68%
5	EtOH	MW, 140°C	3	54%

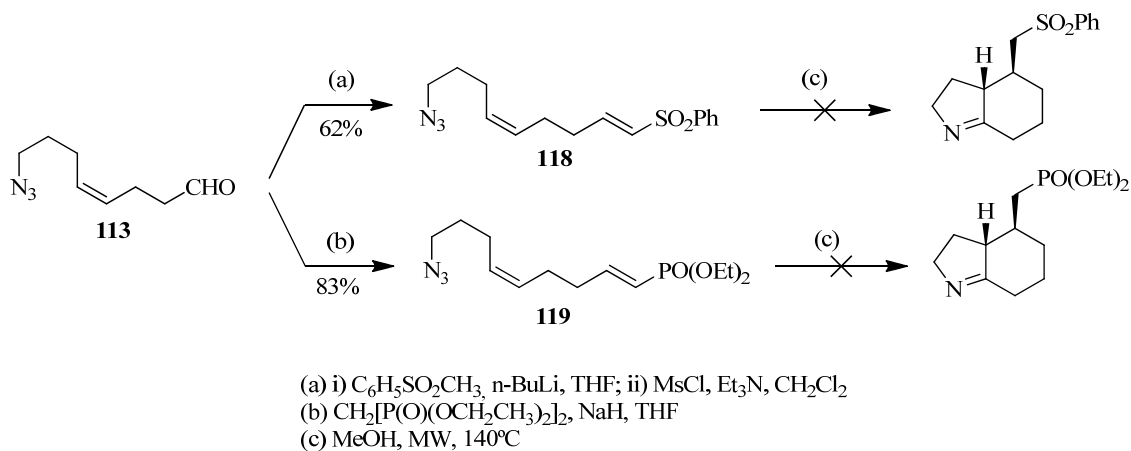
[a] Rendimiento obtenido tras purificar en columna cromatográfica.

La reacción del aldehído **113** con cianometilfosfonato de dietilo condujo con buen rendimiento al producto **116** como mezcla de isómeros *E/Z* que no fue posible separar (Esquema 2.57). A continuación, el calentamiento de una disolución de la mezcla de isómeros en metanol a 140°C en el microondas condujo con éxito al correspondiente derivado de hexahidroindol **117** como un único diastereoisómero con configuración relativa *anti*.



Esquema 2.57. Síntesis y ciclación del azido alqueno **116**.

Se sintetizaron también la vinil sulfona **118** y el vinil fosfonato **119** a partir del correspondiente aldehído **113** empleando los mismos métodos que en ocasiones anteriores para formar estos dobles enlaces electrón-deficientes (Esquema 2.58). Sin embargo, al intentar ciclar dichos azido alquenos en metanol bajo radiación de microondas no se obtuvieron las correspondientes iminas bicyclicas. En el caso de la sulfona el calentamiento de una disolución del compuesto **118** condujo a la formación de un producto cuya estructura no pudo dilucidarse en base a los espectros de RMN ni datos de espectrometría de masas. Por otro lado la reacción del vinil fosfonato **119** en MeOH a 140°C en el microondas produjo la descomposición del mismo antes de que pudiese tener lugar la adición de la enamina sobre el aceptor de Michael.⁷⁰

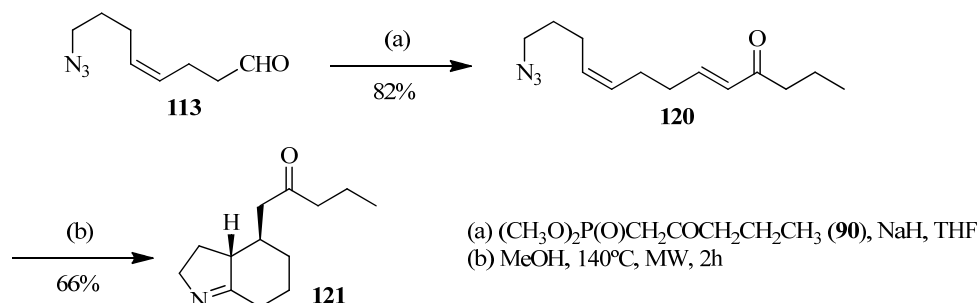


Esquema 2.58. Síntesis y ciclación de los azido alquenos **118** y **119**.

En este punto se decidió volver a probar con cetonas α,β -insaturadas para comprobar si las ceto iminas fusionadas son lo suficientemente estables para poder ser purificadas, a diferencia de las no fusionadas. Así en primer lugar se preparó el azido alqueno **120** empleando el fosfonato **90** previamente sintetizado (Esquema 2.59). Al calentar una disolución de este producto en metanol a 140°C en el microondas durante 2 horas se obtuvo la correspondiente

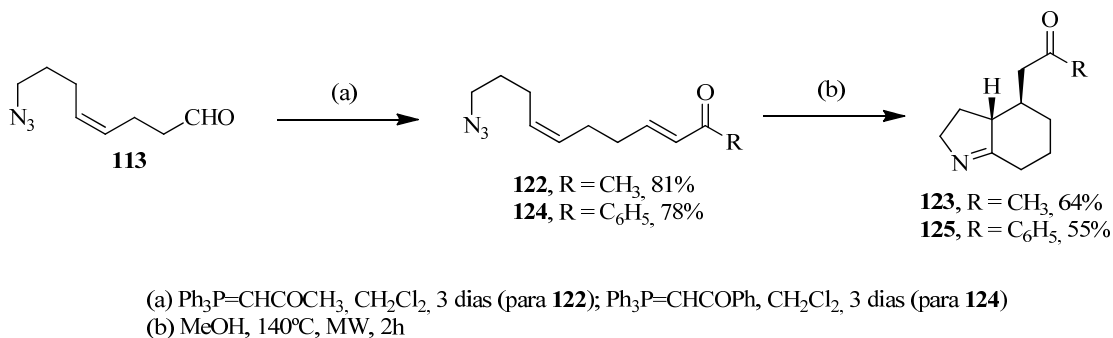
⁷⁰ Posiblemente la menor reactividad de la enamina endocíclica y de los vinil fosfonatos en comparación con otros aceptores de Michael, hace que la adición no sea posible en este caso.

imina bicíclica **121** que pudo ser purificada por cromatografía en columna. Dicho producto se obtuvo con un rendimiento de 66% y de forma completamente diastereoselectiva. Dado el buen resultado, se procedió a preparar otras enonas con las que llevar a cabo la reacción en cascada y comprobar así la generalidad de la reacción con las cetonas α,β -insaturadas.



Esquema 2.59. Síntesis y ciclación de la enona **120**.

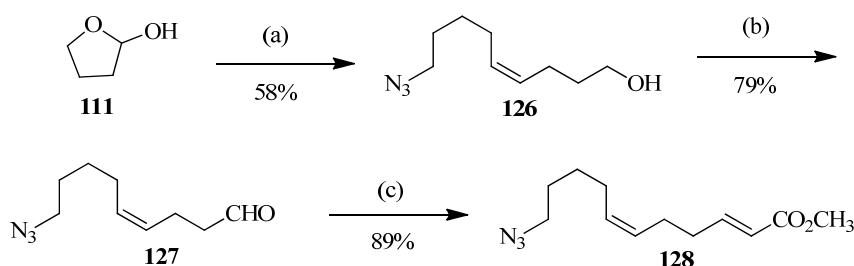
La reacción del aldehído **113** con la 1-(trifenilfosforaniliden)-2-propanona condujo tras tres días de reacción en CH_2Cl_2 al producto **122** el cual al ser calentado en MeOH durante dos horas a 140°C bajo radiación de microondas dio como resultado la correspondiente imina **123** con un rendimiento del 64% (Esquema 2.60). Igualmente se preparó la fenil vinil cetona **124** por reacción del mismo aldehído con 1-fenil-2-(trifenilfosforaniliden)etanona a partir de la cual se obtuvo también la imina fusionada deseada **125** con un rendimiento similar.



Esquema 2.60. Síntesis y ciclación de las enonas **122** y **124**.

2.2.2.4.- Síntesis de piperideinas con estructuras tipo 2,3,4,4a,5,6,7,8-octahidroquinolina.

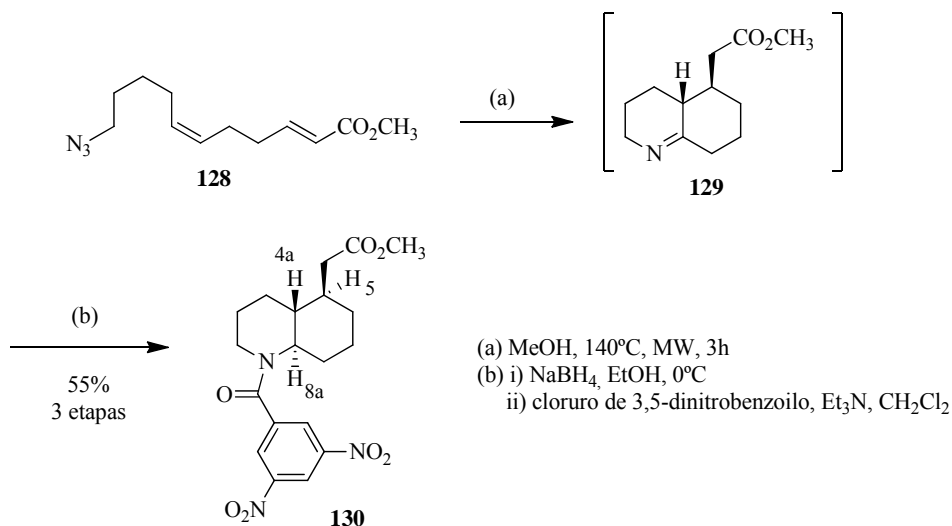
Por último se planteó la síntesis de 1-piperideinas fusionadas, con estructuras de tipo 2,3,4,4a,5,6,7,8-octahidroquinolina. Con este objetivo en mente se preparó el éster metílico **128** siguiendo la metodología ya puesta a punto para la preparación de estos azido alquenos partiendo del lactol **111** (Esquema 2.61). Por reacción de Wittig con la sal de fosfonio **6** se obtuvo el alcohol **126**, el cual se oxidó con PCC y se hizo reaccionar con 2-(trifenilfosforaniliden)acetato de metilo obteniéndose el producto **128** con buen rendimiento.



(a) sal de fosfonio **6** KHMDS, THF/CH₂Cl₂ (9:1), -78°C; (b) PCC, CH₂Cl₂; (c) PH₃P=CHCO₂CH₃, CH₂Cl₂

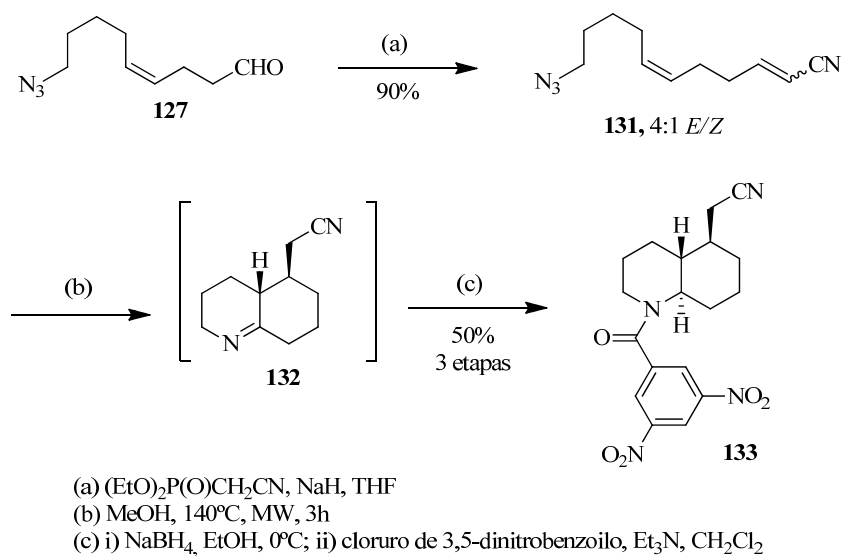
Esquema 2.61. Síntesis del compuesto **128**.

La ciclación del compuesto **128** se llevó a cabo en el reactor microondas a 140°C durante 3 horas empleando MeOH como disolvente (Esquema 2.62). En el espectro de ¹H-RMN del crudo de reacción se pudieron observar las señales del producto esperado, el imino éster **129**. Sin embargo al intentar purificarlo, éste se descompuso, debido a la ya conocida tendencia a oxidarse de este tipo de iminas. Se decidió por tanto llevar a cabo la reducción de la misma directamente con NaBH₄ para luego acilar la amina intermedia obtenida empleando cloruro de 3,5-dinitrobenzoilo en presencia de Et₃N en CH₂Cl₂. De este modo se obtuvo la amida **130** como un único diastereoisómero que sí pudo purificarse y caracterizarse sin problema. En cuanto a su estereoquímica relativa, ésta pudo asignarse en base al espectro NOESY en el que se observa el pico de cruce entre los protones 5 y 8a, pero no se observa señal de estos protones con el 4a.



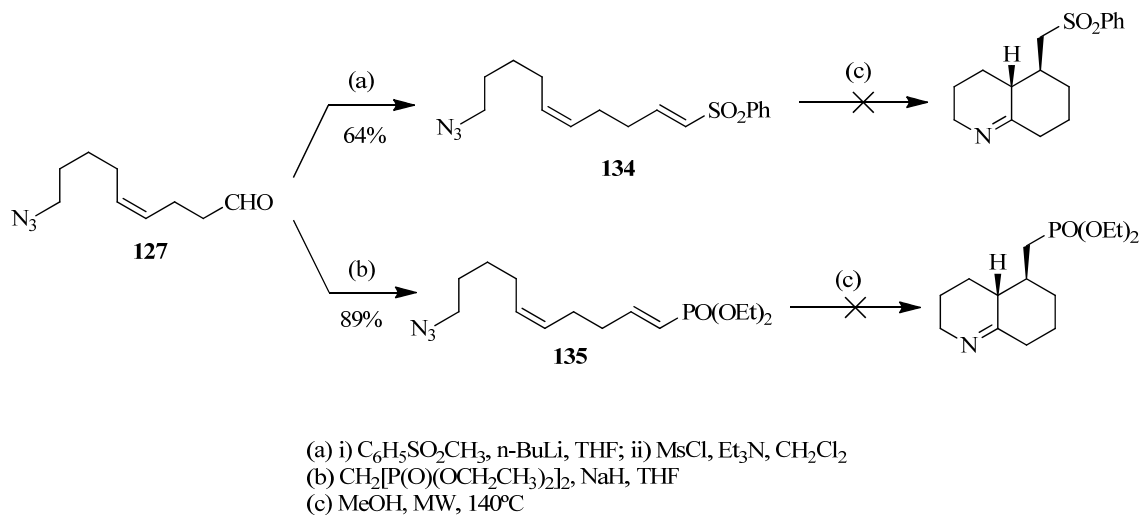
Esquema 2.62. Síntesis de la amida **130**.

A continuación se preparó también la amida análoga con un grupo ciano a partir de la ciclación del compuesto **131** (Esquema 2.63). En este caso de nuevo se pudo introducir el aceptor de Michael sin dificultad y con buen rendimiento obteniéndose el azido alqueno como una mezcla de isómeros *E/Z*. Posteriormente el calentamiento en microondas de una disolución de ambos isómeros en metanol condujo a la imina **132** que no pudo ser purificada debido a su inestabilidad. Su reducción estereoselectiva y posterior acilación de la amina, condujo a la amida **133** de nuevo como un único diastereoisómero.



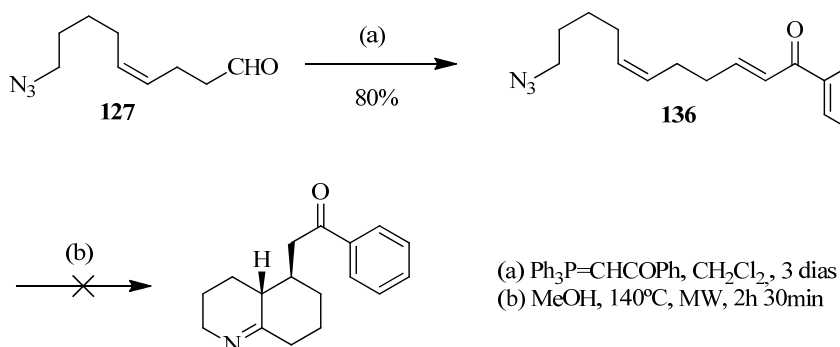
Esquema 2.63. Síntesis de la amida **133**.

Se prepararon también los azido alquenos con una vinil sulfona y un vinil fosfonato como aceptores de Michael, los productos **134** y **135** respectivamente (Esquema 2.64). Desafortunadamente, como ocurrió con las pirrolinas fusionadas, la reacción de ciclación en microondas de estos azido alquenos no produjo las iminas esperadas.



Esquema 2.64. Síntesis y ciclación de los azido alquenos **134** y **135**.

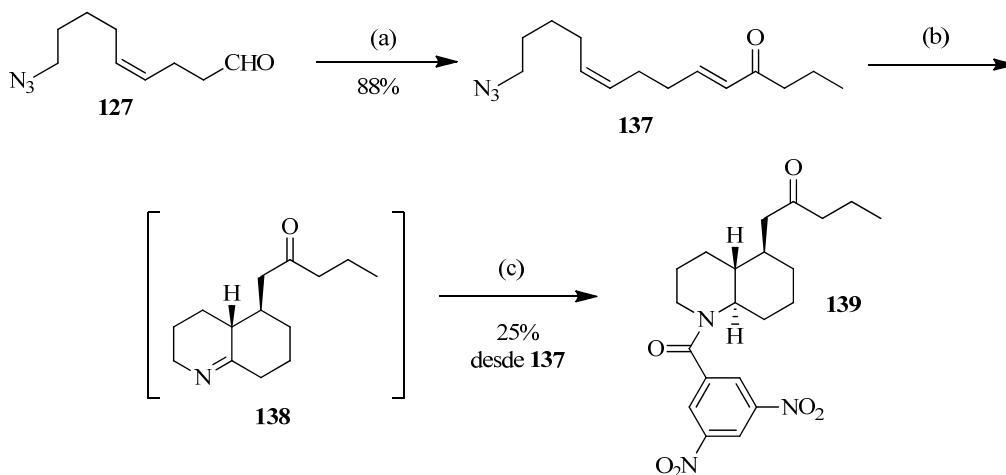
Por último se probó la reacción con cetonas α,β -insaturadas. En primer lugar se preparó la enona **136** por reacción del aldehído **127** con 1-fenil-2-(trifenilfosforaniliden)etanona (Esquema 2.65). A continuación se calentó una disolución de este azido alqueno en metanol a 140°C en el microondas, pero la reacción dio lugar a una compleja mezcla de productos en la que no se identificó la esperada imina.



Esquema 2.65. Síntesis y ciclación del azido alqueno **136**.

Se decidió probar con otra cetona α,β -insaturada y se preparó el compuesto **137** empleando el fosfonato **90** (Esquema 2.66). En este caso al llevar a cabo la ciclación en el microondas a 140°C en metanol se observó la formación de la imina **138**. Sin embargo, dada la

tendencia a la oxidación de esta octahidroquinolina se redujo inmediatamente con NaBH_4 . La reacción de la amina así obtenida con cloruro de 3,5-dinitrobenzoilo en presencia de Et_3N como en ocasiones anteriores, permitió obtener la amida **139** con un total diastereocontrol.



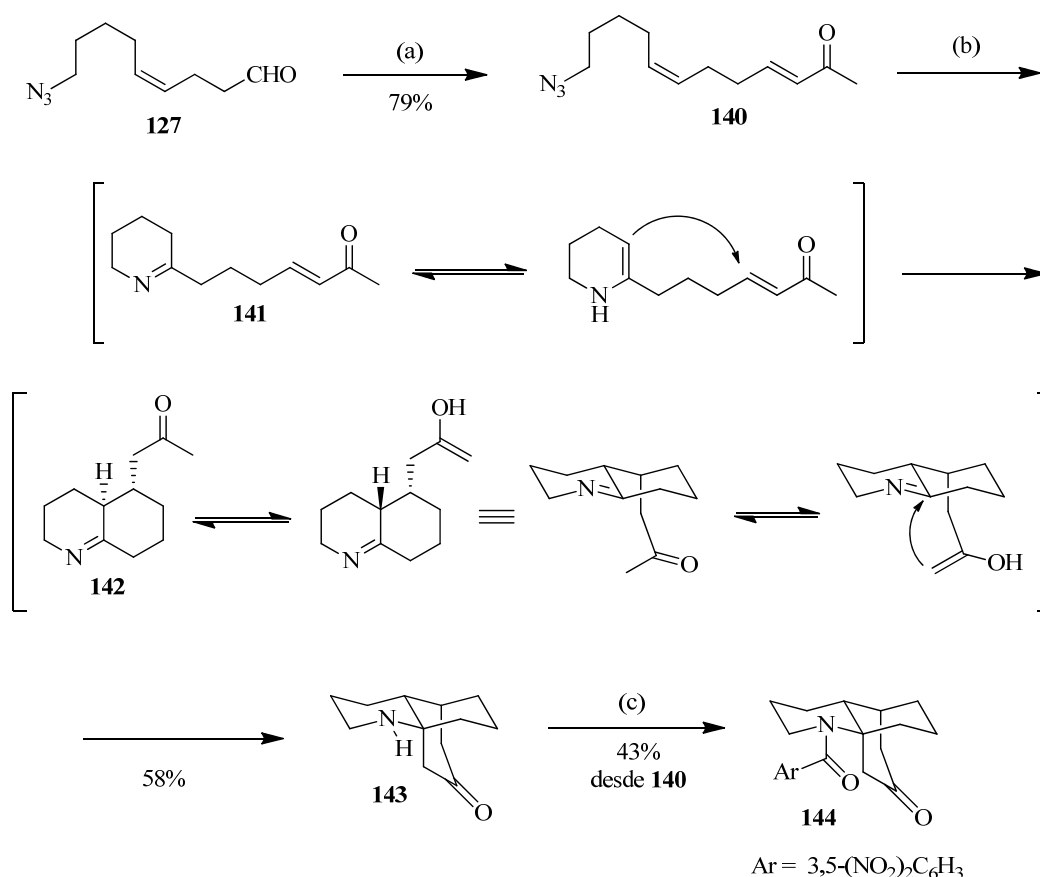
(a) $(\text{CH}_3\text{O})_2\text{P}(\text{O})\text{CH}_2\text{COCH}_2\text{CH}_2\text{CH}_3$ (**90**), NaH , THF, -78°C

(b) MeOH , 140°C , MW, 2h 30min

(c) i) NaBH_4 , EtOH , 0°C ; ii) cloruro de 3,5-dinitrobenzoilo, Et_3N , CH_2Cl_2

Esquema 2.66. Síntesis y ciclación del azido alqueno **137**.

Por último se sintetizó también la enona **140** a partir del aldehído **127** y la 1-(trifenilfosforaniliden)-2-propanona (Esquema 2.67). Sorprendentemente, el calentamiento de una disolución en metanol de dicho compuesto no condujo a la formación de la imina **142**, sino a la amina **143** como un único diastereoisómero. La obtención de esta amina tricíclica se explica mediante una reacción de Mannich intramolecular a partir de la ceto imina intermedia **142**. Por tanto en este caso se trata de una triple reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición de Michael/reacción de Mannich con la que se forman en una sola etapa de reacción tres nuevos ciclos y tres centros estereogénicos nuevos, uno de ellos un carbono cuaternario, y todo ello de manera estereoselectiva.



(a) Ph₃P=CHCOCH₃, CH₂Cl₂, 3 días
 (b) MeOH, 140°C, MW, 3h
 (c) i) NaBH₄, EtOH, 0°C; ii) cloruro de 3,5-dinitrobenzoilo, Et₃N, CH₂Cl₂

Esquema 2.67. Síntesis de los productos **143** y **144** mediante triple reacción en cascada.

Seguidamente se hizo reaccionar esta amina con cloruro de 3,5-dinitrobenzoilo obteniéndose así la amida **144** como un sólido blanco del cual se pudieron obtener cristales válidos para realizar un análisis de difracción de rayos X confirmándose de esta manera la estereoquímica del producto (Figura 2.4).⁷¹

A pesar de que la reacción de Mannich sólo tiene lugar en estas condiciones con la metil cetona, éste es un resultado esperanzador que abre las puertas a seguir investigando y ensayando condiciones que permitan llevar a cabo una triple reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición de Michael/reacción de Mannich con otras azido dienonas.

⁷¹ Los datos de difracción de rayos X del compuesto **144** se encuentran en el anexo II.

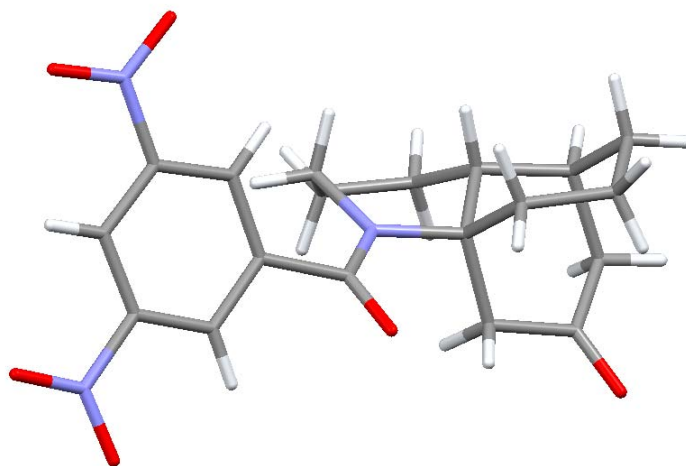


Figura 2.4. Estructura de rayos X del compuesto **144**.

Se ha demostrado por tanto que es posible sintetizar policiclos nitrogenados diferentemente funcionalizados mediante reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición de enamina empleando diferentes electrófilos con los que las iminas cíclicas son capaces de reaccionar en su forma tautomérica de enamina.

PARTE EXPERIMENTAL

2.3.- PARTE EXPERIMENTAL.

A continuación se presenta la parte experimental correspondiente al capítulo de reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición de enamina. Tanto los procedimientos como la caracterización de los productos están redactados en inglés. Todas las reacciones con reactivos sensibles se realizaron en atmósfera inerte (argón) y con disolventes secos. La mayoría de los reactivos utilizados se adquirieron en Aldrich o Fluka y se usaron sin purificar.

2.3.1.- Técnicas generales utilizadas.

Cromatografía

Las cromatografías en capa fina (CCF) se realizaron empleando placas de gel de sílice (Merck, 60 F_{4/254}) de 0,2 mm de espesor, visualizándose las manchas con luz UV (365 nm y 254 nm) o mediante reveladores químicos como ácido fosfomolibdico, permanganato potásico o ninhidrina.

Las cromatografías en columna se realizaron con gel de sílice (Merck, 230-240 mesh ASTM) utilizando la técnica de columna seca con elución a presión (Flash chromatography).¹ El eluyente empleado es indicado en cada caso.

Resonancia magnética nuclear²

Los espectros de resonancia magnética nuclear fueron realizados en los siguientes equipos: Varian-UNITY-500, Varian-INOVA-400, Varian-MERCURY-400, Varian-INOVA-300 y Bruker-300. Los desplazamientos químicos se describen en partes por millón (δ) y las constantes de acoplamiento (J) se indican en hertzios (Hz). Los espectros de ¹H-RMN están referenciados respecto a la señal residual de protón del disolvente deuterado empleado en cada caso. La asignación de los distintos protones se hizo en base a experimentos bidimensionales tipo COSY, HSQC, HMBC y NOESY empleando la secuencia de pulsos estándar para cada uno de ellos. Cuando fue posible los protones diastereotópicos fueron designados con las letras α y β sin que deba considerarse como asignación estereoquímica de los mismos por analogía con la nomenclatura de esteroides. Los sistemas de spin complejos (2° orden; $\Delta\nu/J < 10$) fueron analizados como tales y las constantes de acoplamiento entre los distintos protones del sistema se calcularon cuando fue posible. Los espectros de ¹³C-RMN, desacoplados de protón en todos los casos, están referenciados respecto al desplazamiento químico de los correspondientes

¹ W. C. Still; M. Khan; A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923-2925.

² T. D. W. Timothy en *High-resolution NMR techniques in organic chemistry*, Elsevier, **2009**.

disolventes deuterados. La asignación de los distintos carbonos se hizo en algunos casos, basándose en experimentos bidimensionales tipo HSQC y HMBC. Si no se indica de otro modo, todos los espectros se registraron a temperatura ambiente.

Infrarrojo

Los espectros de infrarrojo (IR) se registraron en un espectrofotómetro modelo Perkin-Elmer-Spectrum One FT-IR. Las frecuencias del espectro se indican en cm^{-1} .

Espectros de masas

Los espectros de masa exacta de los compuestos fueron obtenidos con un espectrómetro de masas modelo Agilent 6520-Accurate-Mass LC/MS Q-TOF.

Puntos de fusión

Los puntos de fusión se midieron en una aparato de platina calentable tipo Kofler y están sin corregir.

Rayos X

La difracción de rayos X se realizó en el Servicio Interdepartamental de Investigación (SIdI) de la Universidad Autónoma de Madrid.

Microondas

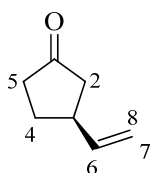
Las reacciones llevadas a cabo en microondas se hicieron en un equipo CEM Discover equipado con agitación electromagnética y un sistema de control de la temperatura y la potencia.

2.3.2.- Synthesis of polycyclic imino alcohols.

2.3.2.1.- Synthesis of tricyclic imino alcohols.

Synthesis of 3-vinylcyclopentanone (1).

Vinylmagnesium bromide (21.0 mL, 1.0 M in THF, 21.0 mmol) and HMPA (7.0 mL) were added to a suspension of $\text{CuBr} \cdot \text{Me}_2\text{S}$ (307 mg, 1.5 mmol) in dry THF (40 mL) at -78°C over 10 minutes. After stirring at -78°C for 15 minutes, a solution of 2-cyclopenten-1-one (821 mg, 10.0 mmol) and TMSCl (6.25 mL, 50.0 mmol) in dry THF (22 mL) was added dropwise over 30 minutes. The reaction mixture was stirred at -78°C for 2 hours, and then quenched by the addition of saturated NH_4Cl (15 mL). The reaction mixture was extracted with EtOAc (3 X 40 mL), the combined organic phases were dried over MgSO_4 , filtered, and concentrated in vacuo. Flash chromatography (silica gel, gradient from hexanes to 7:3 hexanes/ EtOAc) yielded compound **1** as a pale yellow oil (913 mg, 83%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.80 (ddd, 1H, $J_{6,8} = 17.2$, $J_{6,7} = 10.4$, $J_{6,3} = 6.7$, $J = 1.7$ Hz, H-6), 5.02 (m, 2H, H-7 and H-8), 2.79 (m, 1H, H-3), 2.34 (dd, 1H, $J_{2\alpha,2\beta} = 18.0$, $J_{2\alpha,3} = 7.6$ Hz, H-2 α), 2.24 (m, 1H, H-5 α), 2.14 (m, 2H, H-5 β and H-4 α), 1.98 (dd, 1H, $J_{2\beta,2\alpha} = 18.0$, $J_{2\beta,3} = 10.1$ Hz, H-2 β), 1.68 (m, 1H, H-4 β).

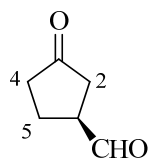
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 218.6 (C=O), 140.4 ($\text{CH}=\text{CH}_2$), 114.3 ($\text{CH}=\text{CH}_2$), 44.3 (C-2), 40.6 (C-3), 38.1 (C-5), 29.4 (C-4).

FTIR (neat) ν_{max} : 3390, 2958, 2930, 1746, 1640 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_7\text{H}_{11}\text{O}$ $[\text{M}+\text{H}]^+$: 111.0764, found: 111.0762.

Ozonolysis of 1. Synthesis of 3-oxocyclopentanecarbaldehyde (2).

Ozone gas was bubbled through a solution of **1** (900 mg, 8.18 mmol) in CH_2Cl_2 (40 mL) at -78°C . After the solution turned blue the reaction mixture was flushed with oxygen until clear. Triphenylphosphine (4.29 g, 16.36 mmol) was added and the mixture was allowed to warm to room temperature overnight. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 1:1 hexanes/ EtOAc) to provide compound **2** as a colorless oil (852 mg, 93%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 9.69 (s, 1H, CHO), 3.15 (m, 1H, H-1), 2.47 (dd, 1H, $J_{2\alpha,2\beta} = 18.6$, $J_{2\alpha,1} = 7.5$ Hz, H-2 α), 2.29 (dd, 1H, $J_{2\beta,2\alpha} = 18.6$, $J_{2\beta,1} = 8.5$ Hz, H-2 β), 2.17 (m, 4H, 2H-4 and 2H-5).

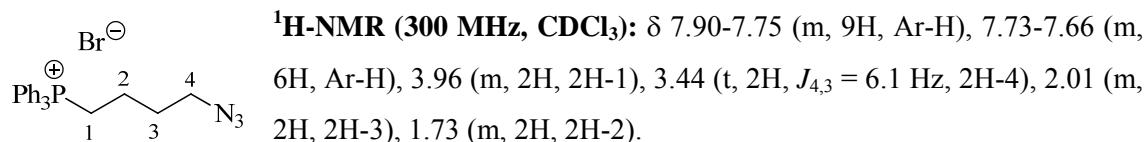
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 216.0 (C=O), 201.0 (CHO), 48.1 (C-1), 37.5 (C-2), 36.9 (C-4), 23.0 (C-5).

FTIR (neat) ν_{\max} : 3426, 1741, 1739 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_6\text{H}_9\text{O}_2$ $[\text{M}+\text{H}]^+$: 113.0603, found: 113.0605

Synthesis of phosphonium salt (4-azidobutyl)triphenylphosphonium bromide (4).

1,4-dibromobutane (35 g, 162 mmol) was dissolved in 150 mL of toluene. Triphenylphosphine (21.2 g, 81 mmol) was added and the mixture was refluxed overnight. Then the solution was concentrated in vacuo and the residue was filtered. The white solid was washed with toluene and dried before using in the next step. The (4-bromobutyl)triphenylphosphonium bromide obtained (29 g, 60.6 mmol) was dissolved in EtOH/ H_2O (200 mL, 1:1) and NaN_3 (19.7 g, 303 mmol) was added. The mixture was heated at 100°C for 12 hours. Then the solvent was removed. The residue was extracted with CH_2Cl_2 (3 X 100 mL) and the combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. The (4-azidobutyl)triphenylphosphonium bromide **4** was obtained as an oil that crystallized as a white solid after several days (23 g, 64% 2 steps).



^{13}C -NMR (75 MHz, CDCl_3): δ 136.1 (d, 3C, $J_{\text{C,P}} = 3$ Hz, Ar-C), 133.8 (d, 6C, $J_{\text{C,P}} = 10$ Hz, Ar-C), 130.6 (d, 6C, $J_{\text{C,P}} = 12$ Hz, Ar-C), 118.4 (d, 3C, $J_{\text{C,P}} = 86$ Hz, Ar-C), 50.7 (C-4), 29.3 (d, $J_{\text{C,P}} = 17$ Hz, C-3), 22.0 (d, $J_{\text{C,P}} = 51$ Hz, C-1), 20.0 (d, $J_{\text{C,P}} = 4$ Hz, C-2).

FTIR (KBr) ν_{\max} : 3434, 2088, 1995, 1631, 1438, 1288, 1112, 996, 753, 743, 723, 690 cm^{-1} .

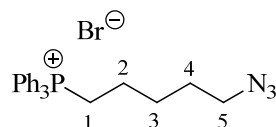
HRMS-ESI (m/z): calcd for $\text{C}_{22}\text{H}_{23}\text{N}_3\text{P}$ $[\text{M}]^+$: 360.1624, found: 360.1630

Mp: 116-119 $^\circ\text{C}$

Synthesis of phosphonium salt (5-azidobutyl)triphenylphosphonium bromide (6).

1,5-dibromopentane (40 g, 174 mmol) was dissolved in 200 mL of toluene. Triphenylphosphine (22.8 g, 87 mmol) was added and the mixture was refluxed overnight. Then the solution was concentrated in vacuo and the residue was filtered. The white solid was washed with toluene and then dissolved in acetone. The acetone was removed and (5-bromopentyl)triphenylphosphonium bromide was obtained as an orange oil. The (5-bromopentyl)triphenylphosphonium bromide (22 g, 44.7 mmol) was then dissolved in EtOH/ H_2O (200 mL, 1:1) and NaN_3 (14.5 g, 223 mmol) was added. The mixture was heated at 100°C for 12 hours. Then the solvent was removed. The residue was extracted with CH_2Cl_2 (3 X

100 mL) and the combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, gradient from CH_2Cl_2 to 9:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to provide compound **6** as a white solid (20.5 g, 52%, 2 steps).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.89-7.73 (m, 9H, Ar-H), 7.72-7.63 (m, 6H, Ar-H), 3.86 (m, 2H, 2H-1), 3.2 (t, 2H, $J_{5,4} = 6.6$ Hz, 2H-5), 1.79-1.54 (m, 6H, 2H-2, 2H-3 and 2H-4).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 135.1 (d, 3C, $J_{\text{C,P}} = 3$ Hz, Ar-C), 133.7 (d, 6C, $J_{\text{C,P}} = 10$ Hz, Ar-C), 130.6 (d, 6C, $J_{\text{C,P}} = 13$ Hz, Ar-C), 118.4 (d, 3C, $J_{\text{C,P}} = 86$ Hz, Ar-C), 51.1 (C-5), 28.4 (C-3), 27.5 (d, $J_{\text{C,P}} = 17$ Hz, C-4), 22.6 (d, $J_{\text{C,P}} = 51$ Hz, C-1), 22.3 (d, $J_{\text{C,P}} = 4$ Hz, C-2).

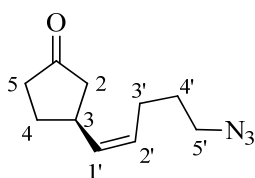
FTIR (KBr) ν_{max} : 3435, 2094, 1631, 1436, 1113, 750, 723, 692 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{23}\text{H}_{25}\text{N}_3\text{P}$ $[\text{M}]^+$: 374.1781, found: 374.1790

Mp: 109-112°C

Wittig reaction. Synthesis of (Z)-3-(5-azidopent-1-en-1-yl)cyclopentanone (7).

To a solution of phosphonium salt **4** (2.35 g, 5.36 mmol) in dry THF (30 mL) was added KHMDS (10.72 mL, 5.36 mmol, 0.5 M solution in toluene) at -78°C . After the reaction mixture was stirred for 30 minutes at -78°C , a solution of aldehyde **2** (400 mg, 3.57 mmol) in dry THF (20 mL) was added dropwise over 20 minutes. After 50 minutes, the reaction mixture was warmed to room temperature over 1 hour. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) yielded compound **7** as a colorless oil (564 mg, 82%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.38 (m, 2H, H-1' and H-2'), 3.28 (t, 2H, $J_{5',4'} = 6.7$ Hz, 2H-5'), 3.09 (m, 1H, H-3), 2.42-2.26 (m, 2H, H-2 α and H-5 α), 2.20-2.10 (m, 4H, 2H-3', H-2 β and H-4 α), 1.91 (ddd, 1H, $J_{5\beta,5\alpha} = 18.2$, $J = 10.5$, $J = 1.2$ Hz, H-5 β), 1.65 (m, 3H, 2H-4' and H-4 β).

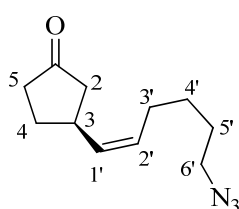
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 219.1 (C=O), 133.7 (C-1'), 129.0 (C-2'), 50.7 (C-5'), 45.4 (C-2), 38.4 (C-5), 35.2 (C-3), 30.4 (C-4), 28.8 (C-4'), 24.6 (C-3').

FTIR (neat) ν_{max} : 3350, 2956, 2099, 1742, 1257 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{10}\text{H}_{16}\text{NO}$ $[\text{M}+\text{H}-\text{N}_2]^+$: 166.1226, found: 166.1227

Wittig reaction. Synthesis of (Z)-3-(6-azidohex-1-en-1-yl)cyclopentanone (8).

Phosphonium salt **6** (2.43 g, 5.36 mmol) was dissolved in dry CH_2Cl_2 (3 mL) at room temperature. THF (27 mL) was added and the mixture was cooled to -78°C . Then KHMDS (10.72 mL, 5.36 mmol, 0.5 M solution in toluene) was added. After the reaction mixture was stirred for 30 minutes at -78°C , a solution of aldehyde **2** (400 mg, 3.57 mmol) in dry THF (20 mL) was added dropwise over 20 minutes. After 50 minutes, the reaction mixture was warmed to room temperature over 1 hour. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) yielded compound **8** as a colorless oil (554 mg, 75%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.35 (m, 2H, H-1' and H-2'), 3.25 (t, 2H, $J_{6',5'} = 6.7$ Hz, 2H-6'), 3.08 (m, 1H, H-3), 2.41-2.25 (m, 2H, H-2 α and H-5 α), 2.22-2.04 (m, 4H, 2H-3', H-2 β and H-4 α), 1.91 (ddd, 1H, $J_{5\beta,5\alpha} = 18.3$, $J = 10.5$, $J = 1.4$ Hz, H-5 β), 1.67-1.54 (m, 3H, 2H-5' and H-4 β), 1.50-1.40 (m, 2H, 2H-4').

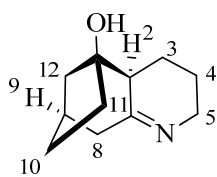
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 219.1 (C=O), 132.8 (C-1'), 130.0 (C-2'), 51.3 (C-6'), 45.4 (C-2), 38.4 (C-5), 35.1 (C-3), 30.3 (C-4), 28.4 (C-5'), 27.1 (C-3'), 26.8 (C-4').

FTIR (neat) ν_{max} : 2935, 2097, 1743 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{11}\text{H}_{17}\text{N}_3\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 230.1262, found: 230.1263

Cyclization of 8. Synthesis of *rac*-(1*S*,2*S*,9*R*)-6-azatricyclo[7.2.1.0^{2,7}]dodec-6-en-1-ol (9).

A solution of compound **8** (200 mg, 0.96 mmol) in DMF (8 mL) was heated in a microwave reactor at 120°C for 3 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The resulting reaction crude was purified by column chromatography (silica gel, gradient from CH_2Cl_2 to 97:3 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford the desired imino alcohol **9** (122 mg, 71%) as a pale yellow oil, whose spectroscopic data was identical to the previous report.³



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 3.73 (m, 1H, H-5 α), 3.45 (m, 1H, H-5 β), 2.57 (m, 2H, H-2 and H-8 α), 2.39 (m, 2H, H-8 β and H-9), 2.09-1.95 (m, 3H, H-3 α , H-4 α and H-12 α), 1.93-1.73 (m, 3H, H-11 α , H-12 β and H-3 β), 1.64-1.36 (m, 4H, H-4 β , H-11 β and 2H-10).

³ M. Movassaghi, B. Chen, *Angew. Chem. Int. Ed.* **2007**, 46, 565-568.

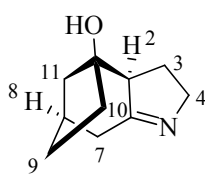
^{13}C -NMR (75 MHz, CDCl_3): δ 170.5 (C=N), 81.3 (C-1), 50.9 (C-2), 49.7 (C-5), 47.2 (C-12), 45.6 (C-8), 33.3 (C-10), 32.0 (C-9), 28.3 (C-11), 21.9 (C-4), 20.8 (C-3).

FTIR (neat) ν_{max} : 3416, 2941, 1653, 1446, 1320 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{11}\text{H}_{18}\text{NO}$ $[\text{M}+\text{H}]^+$: 180.1388, found: 180.1378

Cyclization of 7. Synthesis of *rac*-(1*S*,2*S*,8*R*)-5-azatricyclo[6.2.1.0^{2,6}]undec-5-en-1-ol (**11**).

DBU (0.23 mL, 1.54 mmol) was added to a solution of compound **7** (100 mg, 0.51 mmol) in DMF/ethanol (6 mL, 4:1). The mixture was heated in a microwave reactor at 120°C for 3 hours. The dark brown solution was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, gradient from CH_2Cl_2 to 97:3 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford the desired imino alcohol **11** (68 mg, 81%) as a pale yellow viscous oil, whose spectroscopic data was identical to the previous report.³



^1H -NMR (300 MHz, CDCl_3): δ 3.92 (m, 1H, H-4 α), 3.66 (m, 1H, H-4 β), 3.02 (m, 1H, H-2), 2.43 (m, 2H, H-7 α and H-8), 2.24 (m, 1H, H-7 β), 2.04 (m, 2H, H-3 α and H-11 α), 1.93 (m, 1H, H-11 β), 1.72 (m, 3H, H-3 β , H-9 α and H-10 α), 1.42 (m, 1H, H-10 β), 1.25 (m, 1H, H-9 β).

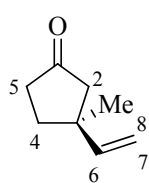
^{13}C -NMR (75 MHz, CDCl_3): δ 177.3 (C=N), 81.2 (C-1), 60.8 (C-2), 59.3 (C-4), 45.8 (C-11), 38.4 (C-7), 33.5 (C-8), 31.3 (C-9), 28.0 (C-10), 23.3 (C-3).

FTIR (neat) ν_{max} : 3205, 2933, 1649, 1451, 990 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{10}\text{H}_{16}\text{NO}$ $[\text{M}+\text{H}]^+$: 166.1226, found: 166.1228

Synthesis of 3-methyl-3-vinylcyclopentanone (**12**).

Vinylmagnesium bromide (21.84 mL, 1.0 M in THF, 21.84 mmol) and HMPA (10.8 mL) were added to a suspension of $\text{CuBr}\cdot\text{SMe}_2$ (320 mg, 1.56 mmol) in dry THF (40 mL) at -78°C over 10 minutes. After stirring at -78°C for 15 minutes, a solution of 3-methyl-2-cyclopenten-1-one (1 g, 10.4 mmol) and TMSCl (6.5 mL, 52 mmol) in dry THF (20 mL) was added dropwise over 30 minutes. The reaction mixture was stirred at -78°C for 2 hours, and then quenched by the addition of saturated NH_4Cl (15 mL). The reaction mixture was extracted with EtOAc (3 X 40 mL), the combined organic phases were dried over MgSO_4 , filtered, and concentrated in vacuo. Flash chromatography (silica gel, gradient from hexanes to 7:3 hexanes/ EtOAc) yielded compound **12** as a pale yellow oil (902 mg, 70%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.85 (dd, 1H, $J_{6,8} = 17.2$, $J_{6,7} = 10.8$ Hz, H-6), 4.96 (m, 2H, H-7 and H-8), 2.29 (d, 1H, $J_{2\alpha,2\beta} = 17.7$ Hz, H-2 α), 2.25 (m, 2H, H-4 α and H-5 α), 2.03 (d, 1H, $J_{2\beta,2\alpha} = 17.7$ Hz, H-2 β), 1.94 (m, 1H, H-5 β), 1.78 (m, 1H, H-4 β), 1.16 (s, 3H, CH_3).

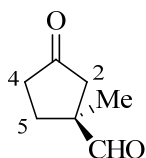
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 219.1 (C=O), 145.5 ($\text{CH}=\text{CH}_2$), 112.0 ($\text{CH}=\text{CH}_2$), 51.1 (C-2), 42.5 (C-5), 36.9 (C-4), 35.3 (C-3), 25.9 (CH_3).

FTIR (neat) ν_{max} : 3392, 2959, 2929, 1744, 1639, 1405, 1165, 915 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_8\text{H}_{13}\text{O}$ $[\text{M}+\text{H}]^+$: 125.0961, found: 125.0960

Ozonolysis of 12. Synthesis of 1-methyl- 3-oxocyclopentanecarbaldehyde (13).

A solution of **12** (800 mg, 6.44 mmol) in CH_2Cl_2 (40 mL) was ozonized at -78°C . After the solution turned blue the reaction mixture was flushed with oxygen until clear. Triphenylphosphine (3.37 g, 12.88 mmol) was added and the mixture was allowed to warm to room temperature overnight. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) to provide compound **13** as a colorless oil (609 mg, 75%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 9.54 (s, 1H, CHO), 2.63 (d, 1H, $J_{2\alpha,2\beta} = 18.3$ Hz, H-2 α), 2.26 (m, 3H, 2H-4 and H-5 α), 2.00 (d, 1H, $J_{2\beta,2\alpha} = 18.3$ Hz, H-2 β), 1.78 (m, 1H, H-5 β), 1.28 (s, 3H, CH_3).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 216.0 (C=O), 202.6 (CHO), 50.9 (C-2) 45.4 (C-1), 36.4 (C-4), 30.3 (C-5), 20.4 (CH_3).

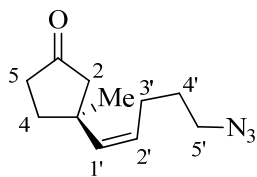
FTIR (neat) ν_{max} : 3424, 2967, 2098, 1745, 1405, 1167, 1120 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_7\text{H}_{14}\text{NO}_2$ $[\text{M}+\text{NH}_4]^+$: 144.1019, found: 144.1017

Wittig reaction. Synthesis of (Z)-3-(5-azidopen-1-en-1-yl)-3-methylcyclopentanone (14).

To a solution of phosphonium salt **4** (1.05 g, 2.38 mmol) in dry THF (25 mL) was added KHMDS (4.76 mL, 2.38 mmol, 0.5 M solution in toluene) at -78°C . After the reaction mixture was stirred for 30 minutes at -78°C , a solution of aldehyde **13** (200 mg, 1.58 mmol) in dry THF (15 mL) was added dropwise over 20 minutes. After 50 minutes the reaction mixture was warmed to room temperature over 1 hour. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column

chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) provided compound **14** (262 mg, 80%) as a colorless oil.



¹H-NMR (300 MHz, CDCl₃): δ 5.52 (dt, 1H, $J_{1',2'} = 11.6$, $J_{1',3'} = 1.8$ Hz, H-1'), 5.26 (dt, 1H, $J_{2',1'} = 11.6$, $J_{2',3'} = 7.4$ Hz, H-2'), 3.29 (t, 2H, $J_{5',4'} = 6.7$ Hz, 2H-5'), 2.39-2.16 (m, 6H, 2H-3', 2H-4 and 2H-2), 2.04 (m, 1H, H-5 α), 1.95 (m, 1H, H-5 β), 1.65 (m, 2H, 2H-4'), 1.24 (s, 3H, CH₃).

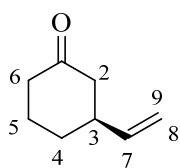
¹³C-NMR (75 MHz, CDCl₃): δ 219.3 (C=O), 138.1 (C-1'), 129.6 (C-2'), 53.1 (C-2), 50.9 (C-5'), 41.0 (C-3), 37.4 (C-5), 36.7 (C-4), 29.1 (C-4'), 26.7 (CH₃), 25.0 (C-3').

FTIR (neat) ν_{\max} : 3351, 2957, 2098, 1743, 1454, 1405, 1255, 1169 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₁H₁₇N₃NaO [M+Na]⁺: 230.1264, found: 230.1266

Synthesis of 3-vinylcyclohexanone (**15**).

Vinylmagnesium bromide (20.0 mL, 1.0 M in THF, 20.0 mmol) was added to a suspension of CuBr·Me₂S (307 mg, 1.5 mmol) in dry THF (40 mL) at -78°C over 10 minutes. After stirring at -78°C for 15 minutes, a solution of 2-cyclohexen-1-one (956 mg, 10.0 mmol) and TMSCl (6.25 mL, 50.0 mmol) in dry THF (22 mL) was added dropwise over 30 minutes. The reaction mixture was stirred at -78°C for 2 hours, and then quenched by the addition of saturated NH₄Cl (15 mL). The reaction mixture was extracted with EtOAc (3 X 40 mL), the combined organic phases were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) yielded compound **15** as a pale yellow oil (1.07 g, 86%).



¹H-NMR (300 MHz, CDCl₃): δ 5.75 (ddd, 1H, $J_{7,9} = 19.9$, $J_{7,8} = 10.4$, $J_{7,3} = 6.1$ Hz, H-7), 4.99 (m, 2H, H-8 and H-9), 2.46 (m, 1H, H-3), 2.40 (m, 1H, H-2 α), 2.33-2.17 (m, 3H, H-2 β and 2H-6), 2.02 (m, 1H, H-4 α), 1.90 (m, 1H, H-5 α), 1.66 (m, 1H, H-5 β), 1.49 (m, 1H, H-4 β).

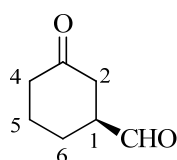
¹³C-NMR (75 MHz, CDCl₃): δ 211.2 (C=O), 141.3 (CH=CH₂), 113.8 (CH=CH₂), 46.9 (C-2), 42.3 (C-3), 41.3 (C-6), 31.0 (C-4), 25.0 (C-5).

FTIR (neat) ν_{\max} : 3951, 2950, 1712, 1635, 1453 cm⁻¹.

HRMS-ESI (m/z): calcd for C₈H₁₂NaO [M+Na]⁺: 147.0786, found: 147.0788

Ozonolysis of 15. Synthesis of 3-oxocyclohexanecarbaldehyde (16).

Ozone gas was bubbled through a solution of **15** (1.0 g, 8.06 mmol) in CH_2Cl_2 (40 mL) at -78°C . After the solution turned blue the reaction mixture was flushed with oxygen until clear. Triphenylphosphine (4.22 g, 16.12 mmol) was added and the mixture was allowed to warm to room temperature overnight. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 1:1 hexanes/EtOAc) to provide compound **16** as a colorless oil (914 mg, 90%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 9.54 (s, 1H, CHO), 2.71 (m, 1H, H-1), 2.38 (m, 2H, H-2 α and H-4 α), 2.22 (m, 2H, H-2 β and H-4 β), 2.05 (m, 1H, H-6 α), 1.93 (m, 1H, H-5 α), 1.75-1.59 (m, 2H, H-6 β and H-5 β).

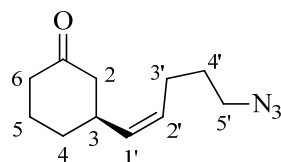
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 209.3 (C=O), 201.2 (CHO), 49.9 (C-1), 40.9 (C-2), 40.0 (C-4), 24.3 (2C, C-5 and C-6).

FTIR (neat) ν_{max} : 2949, 2870, 1715, 1225 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_7\text{H}_{11}\text{O}_2$ $[\text{M}+\text{H}]^+$: 127.0759, found: 127.0760

Wittig reaction. Synthesis of (Z)-3-(5-azidopent-1-en-1-yl)cyclohexanone (17).

To a solution of phosphonium salt **4** (2.09 g, 4.76 mmol) in dry THF (30 mL) was added KHMDS (9.52 mL, 4.76 mmol, 0.5 M solution in toluene) at -78°C . After the reaction mixture was stirred for 30 minutes at -78°C , a solution of aldehyde **16** (400 mg, 3.17 mmol) in dry THF (20 mL) was added dropwise over 20 minutes. After 45 minutes, the reaction mixture was warmed to room temperature over 1 hour. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) yielded compound **17** as a colorless oil (551 mg, 84%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.28 (m, 2H, H-1' and H-2'), 3.24 (t, 2H, $J_{5',4'} = 6.8$ Hz, 2H-5'), 2.74 (m, 1H, H-3), 2.30 (m, 3H, H-2 α and 2H-6), 2.09 (m, 4H, H-2 β , H-4 α and 2H-3'), 1.75 (m, 2H, 2H-5), 1.62 (m, 2H, 2H-4'), 1.48 (m, 1H, H-4 β).

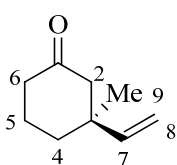
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 210.9 (C=O), 134.0 (C-1'), 128. (C-2'), 50.8 (C-5'), 47.9 (C-2), 41.2 (C-6), 37.4 (C-3), 31.7 (C-4), 28.8 (C-4'), 25.3 (C-5), 24.5 (C-3').

FTIR (neat) ν_{max} : 3401, 2937, 2097, 1712, 1657 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{11}\text{H}_{17}\text{N}_3\text{ONa}$ $[\text{M}+\text{Na}]^+$: 230.1262, found: 230.1263

Synthesis of 3-methyl-3-vinylcyclohexanone (18).

Vinylmagnesium bromide (19.08 mL, 1.0 M in THF, 19.08 mmol) and HMPA (9.4 mL) were added to a suspension of $\text{CuBr} \cdot \text{SMe}_2$ (280 mg, 1.36 mmol) in dry THF (30 mL) at -78°C over 10 minutes. After stirring at -78°C for 15 minutes, a solution of 3-methyl-2-cyclohexen-1-one (1.0 g, 9.08 mmol) and TMSCl (5.66 mL, 45.4 mmol) in dry THF (30 mL) was added dropwise over 25 minutes. The reaction mixture was stirred at -78°C for 2 hours, and then quenched by the addition of saturated NH_4Cl solution (15 mL). The reaction mixture was extracted with EtOAc (3 X 40 mL), the combined organic phases were dried over MgSO_4 , filtered, and concentrated in vacuo. Flash chromatography (silica gel, gradient from hexanes to 7:3 hexanes/ EtOAc) yielded compound **18** as a pale yellow oil (839 mg, 67%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.68 (dd, 1H, $J_{7,9}=17.5$, $J_{7,8}=10.9$ Hz, H-7), 4.96 (m, 2H, H-8 and H-9), 2.42 (d, 1H, $J_{2\alpha,2\beta}=14.0$ Hz, H-2 α), 2.24 (m, 2H, 2H-6), 2.14 (d, 1H, $J_{2\beta,2\alpha}=14.0$ Hz, H-2 β), 1.82 (m, 2H, H-4 α and H-5 α), 1.65 (m, 2H, H-5 β and H-4 β), 1.03 (s, 3H, CH_3).

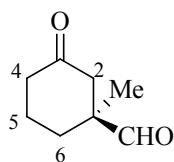
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 211.2 (C=O), 145.7 ($\text{CH}=\text{CH}_2$), 112.6 ($\text{CH}=\text{CH}_2$), 51.6 (C-2), 41.5 (C-3), 40.8 (C-6), 36.5 (C-4), 27.2 (CH_3), 22.0 (C-5).

FTIR (neat) ν_{max} : 3398, 2951, 1712, 1635, 1455 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_9\text{H}_{14}\text{NaO}$ [$\text{M}+\text{Na}$] $^+$: 161.0937, found: 161.0938

Ozonolysis of 18. Synthesis of 1-methyl-3-oxocyclohexanecarbaldehyde (19).

Ozone gas was bubbled through a solution of **18** (700 mg, 5.07 mmol) in CH_2Cl_2 (40 mL) at -78°C . After the solution turned blue the reaction mixture was flushed with oxygen until clear. Triphenylphosphine (2.65 g, 10.14 mmol) was added and the mixture was allowed to warm to room temperature overnight. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 7:3 hexanes/ EtOAc) to provide compound **19** as a colorless oil (632 mg, 89%).



$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 9.40 (s, 1H, CHO), 2.58 (d, 1H, $J_{2\alpha,2\beta}=14.6$ Hz, H-2 α), 2.27 (m, 2H, 2H-4), 2.08 (d, 1H, $J_{2\beta,2\alpha}=14.6$ Hz, H-2 β), 1.99 (m, 2H, H-6 α and H-5 α), 1.77 (m, 1H, H-6 β), 1.63 (m, 1H, H-5 β), 1.12 (s, 3H, CH_3).

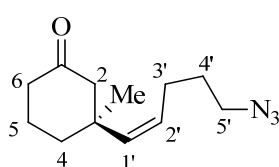
$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 209.1 (C=O), 203.3 (CHO), 50.2 (C-2), 46.7 (C-1), 40.5 (C-4), 30.8 (C-6), 21.7 (C-5), 20.7 (CH_3).

FTIR (neat) ν_{max} : 2948, 2871, 1714, 1224 cm^{-1} .

HRMS-ESI (m/z): calcd for $C_8H_{13}O_2$ $[M+H]^+$: 141.0944, found: 141.0943

Wittig reaction. Synthesis of (Z)-3-(5-azidopent-1-en-1-yl)-3-methylcyclohexanone (20).

To a solution of phosphonium salt **4** (1.18 g, 2.68 mmol) in dry THF (25 mL) was added KHMDS (5.36 mL, 2.68 mmol, 0.5 M solution in toluene) at -78°C . After the reaction mixture was stirred for 30 minutes at -78°C , a solution of aldehyde **19** (250 mg, 1.78 mmol) in dry THF (15 mL) was added dropwise over 20 minutes. After 45 minutes, the reaction mixture was warmed to room temperature over 1 hour. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) yielded compound **20** as a colorless oil (279 mg, 71%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.24 (m, 2H, H-1' and H-2'), 3.28 (t, 2H, $J_{5',4'} = 6.8$ Hz, 2H-5'), 2.46 (d, 1H, $J_{2\alpha,2\beta} = 13.2$ Hz, H-2 α), 2.23 (m, 5H, 2H-3', 2H-6 and H-2 β), 1.87 (m, 3H, 2H-5 and H-4 α), 1.64 (m, 3H, 2H-4' and H-4 β), 1.17 (s, 3H, CH_3).

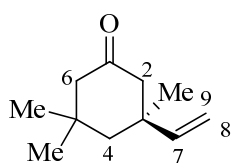
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 211.3 (C=O), 136.7 (C-1'), 129.9 (C-2'), 54.7 (C-2), 50.9 (C-5'), 41.4 (C-3), 40.9 (C-6), 38.0 (C-4), 29.1 (C-4'), 27.6 (CH_3), 25.8 (C-3'), 22.6 (C-5).

FTIR (neat) ν_{max} : 3421, 2938, 2097, 1711, 1658 cm^{-1} .

HRMS-ESI (m/z): calcd for $C_{12}H_{19}N_3\text{NaO}$ $[M+\text{Na}]^+$: 244.1420, found: 244.1423

Synthesis of 3,3,5-trimethyl-5-vinylcyclohexanone (21).

Vinylmagnesium bromide (15.2 mL, 1.0 M in THF, 15.2 mmol) and HMPA (7.5 mL) were added to a suspension of $\text{CuBr} \cdot \text{SMe}_2$ (223 mg, 1.08 mmol) in dry THF (40 mL) at -78°C over 10 minutes. After stirring at -78°C for 15 minutes, a solution of isophorone (1.0 g, 7.23 mmol) and TMSCl (4.6 mL, 36.0 mmol) in dry THF (20 mL) was added dropwise over 30 minutes. The reaction mixture was stirred at -78°C for 2 hours, and then quenched by the addition of saturated NH_4Cl (15 mL). The reaction mixture was extracted with EtOAc (3 X 40 mL), the combined organic phases were dried over MgSO_4 , filtered, and concentrated in vacuo. Flash chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) yielded compound **21** as a pale yellow oil (1.15 g, 96%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.76 (dd, 1H, $J_{7,9} = 17.6$, $J_{7,8} = 10.8$ Hz, H-7), 5.00 (d, 1H, $J_{9,7} = 17.6$ Hz, H-9), 4.92 (d, 1H, $J_{8,7} = 10.8$ Hz, H-8), 2.56 (d, 1H, $J_{2\alpha,2\beta} = 13.4$ Hz, H-2 α), 2.14 (m, 3H, 2H-6 and H-2 β), 1.66 (m, 2H, 2H-4), 1.07 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 0.94 (s, 3H, CH_3).

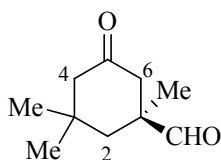
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 211.4 (C=O), 147.1 ($\text{CH}=\text{CH}_2$), 111.8 ($\text{CH}=\text{CH}_2$), 54.3 (C-6), 50.8 (C-4), 49.8 (C-2), 41.5 (C-3), 36.3 (C-5), 33.0 (CH_3), 31.5 (CH_3), 29.3 (CH_3).

FTIR (neat) ν_{max} : 3401, 2957, 1714, 1636, 1457, 1283, 1229, 914 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{11}\text{H}_{19}\text{O}$ $[\text{M}+\text{H}]^+$: 167.1428, found: 167.1428

Ozonolysis of **21**. Synthesis of 1,3,3-trimethyl-5-oxocyclohexanecarbaldehyde (**22**).

A solution of **21** (400 mg, 2.41 mmol) in CH_2Cl_2 (40 mL) was ozonized at -78°C . After the solution turned blue the reaction mixture was flushed with oxygen until clear. Triphenylphosphine (1.26 g, 4.82 mmol) was added and the mixture was allowed to warm to room temperature overnight. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) to provide compound **22** as a white solid (377 mg, 93%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 9.47 (s, 1H, CHO), 2.86 (d, 1H, $J_{6\alpha,6\beta} = 14.8$ Hz, H-6 α), 2.21-2.04 (m, 4H, 2H-2, H-4 α and H-6 β), 1.65 (d, 1H, $J_{4\beta,4\alpha} = 14.5$ Hz, H-4 β), 1.12 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 0.80 (s, 3H, CH_3).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 208.9 (C=O), 203.6 (CHO), 54.0 (C-1), 49.4 (C-2), 45.9 (C-4), 45.4 (C-6), 35.4 (C-3), 32.1 (CH_3), 28.0 (CH_3), 24.6 (CH_3).

FTIR (KBr) ν_{max} : 3395, 2961, 1727, 1461, 1283, 1189, 1162 cm^{-1} .

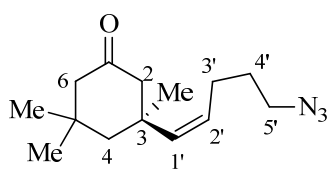
HRMS-ESI (m/z): calcd for $\text{C}_{10}\text{H}_{17}\text{O}_2$ $[\text{M}+\text{H}]^+$: 169.1221, found: 169.1221

Mp: 56-59 $^\circ\text{C}$

Wittig reaction. Synthesis of (Z)-3-(5-azidopent-1-en-1-yl)-3,5,5-trimethylcyclohexanone (**23**).

To a solution of phosphonium salt **4** (785 mg, 1.78 mmol) in dry THF (25 mL) was added KHMDS (3.56 mL, 1.78 mmol, 0.5 M solution in toluene) at -78°C . After the reaction mixture was stirred for 30 minutes at -78°C , a solution of aldehyde **22** (200 mg, 1.19 mmol) in dry THF (15 mL) was added dropwise over 20 minutes. After 50 minutes, the reaction mixture was

warmed to room temperature over 1 hour. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) provided compound **23** as a colorless oil (211 mg, 71%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.34 (d, 1H, $J_{1',2'} = 12.0$ Hz, H-1'), 5.08 (m, 1H, H-2'), 3.25 (t, 2H, $J_{5',4'} = 6.8$ Hz, 2H-5'), 2.43 (d, 1H, $J_{2\alpha,2\beta} = 13.3$ Hz, H-2 α), 2.29-2.02 (m, 5H, 2H-3', 2H-6 and H-2 β), 1.90 (d, 1H, $J_{4\alpha,4\beta} = 15.2$ Hz, H-4 α), 1.60 (m, 3H, 2H-4' and H-4 β), 1.17 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.91 (s, 3H, CH_3).

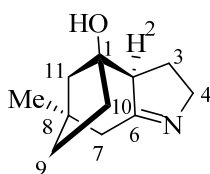
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 211.3 (C=O), 137.8 (C-1'), 128.6 (C-2'), 54.3 (C-6), 54.0 (C-2), 50.9 (2C, C-4 and C-5'), 40.8 (C-3), 36.3 (C-5), 32.8 (CH_3), 31.0 (CH_3), 29.1 (CH_3), 28.9 (C-4'), 25.7 (C-3').

FTIR (neat) ν_{max} : 3394, 2956, 2929, 2868, 2098, 1714, 1456, 1281 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{14}\text{H}_{23}\text{N}_3\text{NaO}$ $[\text{M}+\text{Na}]^+$: 272.1733, found: 272.1734

Cyclization of **14**. Synthesis of *rac*-(1*S*,2*S*,8*R*)-8-methyl-5-azatricyclo[6.2.1.0^{2,6}]undec-5-en-1-ol (**24**).

DBU (0.22 mL, 1.44 mmol) was added to a solution of compound **14** (100 mg, 0.48 mmol) in DMF/ethanol (10 mL, 4:1). The mixture was heated in a microwave reactor at 120°C for 3 hours. The dark brown solution was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, gradient from CH_2Cl_2 to 95:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford the desired imino alcohol **24** (63 mg, 73%) as a pale yellow viscous oil, whose spectroscopic data was identical to the previous report.³



$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 3.94 (ddd, 1H, $J_{4\alpha,4\beta} = 15.0$, $J = 10.0$, $J = 1.9$ Hz, H-4 α), 3.67 (m, 1H, H-4 β), 2.99 (td, 1H, $J_{2,3} = 9.0$, $J = 2.0$ Hz, H-2), 2.30 (dd, 1H, $J_{7\alpha,7\beta} = 14.4$, $J = 2.2$ Hz, H-7 α), 2.14-2.00 (m, 2H, H-7 β and H-3 α), 1.91 (dd, 1H, $J_{11\alpha,11\beta} = 11.1$, $J = 2.3$ Hz, H-11 α), 1.78-1.65 (m, 3H, H-3 β , H-10 α and H-11 β), 1.63-1.46 (m, 2H, H-10 β and H-9 α), 1.31 (m, 1H, H-9 β), 1.14 (s, 3H, CH_3).

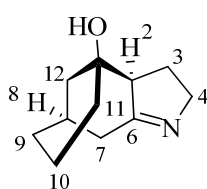
$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 177.4 (C=N), 81.1 (C-1), 60.2 (C-2), 60.0 (C-4), 53.2 (C-11), 45.3 (C-7), 40.2 (C-8), 35.5 (C-9), 32.7 (C-10), 27.0 (CH_3), 23.4 (C-3).

FTIR (neat) ν_{\max} : 3206, 2934, 1650, 1452, 1305, 1265, 1065, 992 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{11}\text{H}_{18}\text{NO}$ $[\text{M}+\text{H}]^+$: 180.1383, found: 180.1382

Cyclization of 17. Synthesis of *rac*-(1*S*,2*S*,8*R*)-5-azatricyclo[6.3.1.0^{2,6}]dodec-5-en-1-ol (25).

DBU (0.22 mL, 1.45 mmol) was added to a solution of compound **17** (100 mg, 0.48 mmol) in DMF/ethanol (10 mL, 4:1). The mixture was heated in a microwave reactor at 120°C for 3 hours. The dark brown solution was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, gradient from CH_2Cl_2 to 97:3 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford the desired imino alcohol **25** (61 mg, 71%) as a pale yellow viscous oil, whose spectroscopic data was identical to the previous report.³



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 3.91 (m, 1H, H-4 α), 3.57 (m, 1H, H-4 β), 2.77 (m, 1H, H-2), 2.56 (m, 1H, H-7 α), 2.42 (m, 2H, H-8 and H-7 β), 2.07 (m, 1H, H-3 α), 1.95 (m, 1H, H-12 α), 1.80 (m, 2H, H-3 β and H-12 β), 1.78-1.68 (m, 1H, H-11 α), 1.66-1.55 (m, 1H, H-11 β), 1.51-1.40 (m, 2H, H-10 α and H-9 α), 1.38-1.28 (m, 2H, H-10 β and H-9 β).

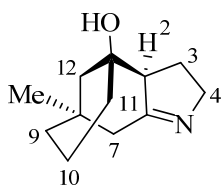
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 179.0 (C=N), 70.6 (C-1), 59.8 (C-2), 58.9 (C-4), 43.9 (C-12), 36.1 (C-7), 35.6 (C-11), 31.4 (2C, C-8 and C-9), 23.7 (C-3), 20.4 (C-10).

FTIR (neat) ν_{\max} : 3201, 2930, 1652, 1449 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{11}\text{H}_{18}\text{NO}$ $[\text{M}+\text{H}]^+$: 180.1383, found: 180.1381

Cyclization of 20. Synthesis of *rac*-(1*S*,2*S*,8*R*)-8-methyl-5-azatricyclo[6.3.1.0^{2,6}]dodec-5-en-1-ol (26).

DBU (0.21 mL, 1.35 mmol) was added to a solution of compound **20** (100 mg, 0.45 mmol) in DMF/ethanol (10 mL, 4:1). The mixture was heated in a microwave reactor at 120°C for 3 hours. The dark brown solution was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, gradient from CH_2Cl_2 to 96:4 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford the desired imino alcohol **26** (67 mg, 77%) as a pale yellow viscous oil.



¹H-NMR (400 MHz, CDCl₃): δ 3.91 (m, 1H, H-4 α), 3.57 (m, 1H, H-4 β), 2.71 (m, 1H, H-2), 2.43 (d, 1H, $J_{7\alpha,7\beta}$ = 15.8 Hz, H-7 α), 2.05 (m, 2H, H-7 β and H-3 α), 1.92 (m, 1H, H-12 α), 1.74-1.63 (m, 3H, H-12 β , H-3 β and H-11 α), 1.55 (m, 1H, H-11 β), 1.45 (m, 1H, H-9 α), 1.33-1.17 (m, 3H, H-9 β and 2H-10), 1.03 (s, 3H, CH₃).

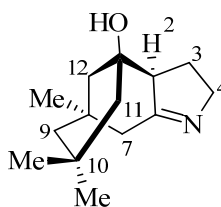
¹³C-NMR (100 MHz, CDCl₃): δ 179.8 (C=N), 71.7 (C-1), 58.8 (C-2), 58.6 (C-4), 50.9 (C-12), 42.8 (C-7), 38.4 (C-8), 35.1 (C-9), 34.7 (C-11), 31.2 (CH₃), 23.0 (C-3), 20.4 (C-10).

FTIR (neat) ν_{\max} : 3202, 2930, 1647, 1454 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₂H₂₀NO [M+H]⁺: 194.1539, found: 194.1541

Cyclization of **23**. Synthesis of *rac*-(1*S*,2*S*,8*R*)-8,10,10-trimethyl-5-azatricyclo[6.3.1.0^{2,6}]dodec-5-en-1-ol (**27**).

DBU (0.18 mL, 1.20 mmol) was added to a solution of compound **23** (100 mg, 0.40 mmol) in DMF/ethanol (10 mL, 4:1). The mixture was heated in a microwave reactor at 120°C for 3 hours. The dark brown solution was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, gradient from CH₂Cl₂ to 98:2 CH₂Cl₂/MeOH) to afford the desired imino alcohol **27** (65 mg, 74%) as a pale yellow viscous oil.



¹H-NMR (400 MHz, CDCl₃): δ 3.97 (ddd, 1H, $J_{4\alpha,4\beta}$ = 15.0, J = 9.3, J = 1.7 Hz, H-4 α), 3.61 (m, 1H, H-4 β), 2.72 (t, 1H, J = 9.5 Hz, H-2), 2.45 (d, 1H, $J_{7\alpha,7\beta}$ = 16.8 Hz, H-7 α), 2.08 (m, 2H, H-3 α and H-7 β), 1.77 (d, 1H, $J_{12\alpha,12\beta}$ = 14.3 Hz, H-12 α), 1.73-1.52 (m, 3H, H-3 β and 2H-11), 1.28 (m, 3H, H-12 β and 2H-9), 1.08 (s, 3H, CH₃), 0.98 (s, 3H, CH₃), 0.86 (s, 3H, CH₃).

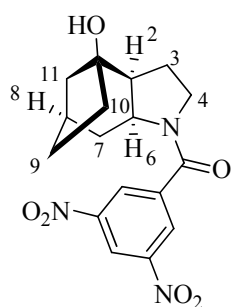
¹³C-NMR (100 MHz, CDCl₃): δ 180.0 (C=N), 73.3 (C-1), 59.5 (C-2), 58.9 (C-4), 51.7 (C-9), 50.4 (C-11), 47.2 (C-12), 42.7 (C-7), 37.8 (CH₃), 35.4 (C-8), 33.2 (CH₃), 31.1 (CH₃), 30.6 (C-10), 24.4 (C-3).

FTIR (neat) ν_{\max} : 3337, 2952, 2926, 2866, 1645, 1463, 1041, 990, 754 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₄H₂₄NO [M+H]⁺: 222.1849, found: 222.1851.

Synthesis of *rac*-(3,5-dinitrophenyl)[(1*S*,2*S*,6*S*,8*R*)-1-hydroxy-5-azatetracyclo[6.2.1.0^{2,6}]undecan-5-yl]methanone (28).

Sodium borohydride (23 mg, 0.60 mmol) was added to a solution of compound **11** (50 mg, 0.30 mmol) in absolute ethanol (5 mL) at 0°C. After 45 minutes the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 X 30 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated in vacuo. The crude material was dissolved in CH₂Cl₂ (10 mL) and cooled to 0°C. Et₃N (82 µL, 0.60 mmol) and 3,5-dinitrobenzoyl chloride (104 mg, 0.45 mmol) were sequentially added. After stirring at room temperature for 8 hours the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from 8:2 to 3:7 hexanes/EtOAc) to afford compound **28** (67 mg, 62 %) as a white solid.



¹H-NMR (400 MHz, CDCl₃): δ 9.10 (t, 1H, *J* = 2.0 Hz, Ar-H), 8.68 (d, 2H, *J* = 2.0 Hz, Ar-H), 4.44 (t, 1H, *J* = 7.9 Hz, H-6), 3.75 (m, 1H, H-4α), 3.39 (m, 1H, H-4β), 2.68 (t, 1H, *J* = 8.9 Hz, H-2), 2.34 (m, 1H, H-7α), 2.28 (dd, 1H, *J*_{3α,3β} = 13.6, *J* = 7.3 Hz, H-3α), 2.12-1.96 (m, 5H, H-8, H-3β, 2H-10 and H-11α), 1.83 (m, 1H, H-7β), 1.60 (m, 1H, H-9α), 1.50 (m, 1H, H-9β), 1.41 (m, 1H, H-11β).

¹³C-NMR (100 MHz, CDCl₃): δ 166.2 (C=O), 148.7 (2C, Ar-C), 140.9 (Ar-C), 127.8 (2C, Ar-C), 120.2 (Ar-C), 79.5 (C-1), 57.3 (C-6), 51.4 (C-4), 49.9 (C-2), 45.3 (C-7), 36.5 (C-11), 33.3 (C-8), 33.2 (C-10), 27.3 (C-9), 27.0 (C-3).

FTIR (KBr) ν_{max}: 3434, 2944, 1626, 1540, 1342 cm⁻¹.

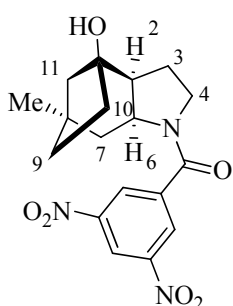
HRMS-ESI (m/z): calcd for C₁₇H₂₀N₃O₆ [M+H]⁺: 362.1352, found: 362.1355

Mp: 199-202°C

Synthesis of *rac*-(3,5-dinitrophenyl)[(1*S*,2*S*,6*S*,8*R*)-1-hydroxy-8-methyl-5-azatetracyclo[6.2.1.0^{2,6}]undecan-5-yl]methanone (29).

Sodium borohydride (21 mg, 0.56 mmol) was added to a solution of compound **24** (50 mg, 0.28 mmol) in absolute ethanol (5 mL) at 0°C. After 45 minutes the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 X 30 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated in

vacuo. The crude material was dissolved in CH_2Cl_2 (10 mL) and cooled to 0°C . Et_3N (76 μL , 0.56 mmol) and 3,5-dinitrobenzoyl chloride (97 mg, 0.42 mmol) were sequentially added. After stirring at room temperature for 8 hours the reaction mixture was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO_4 , filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from 8:2 to 3:7 hexanes/ EtOAc) to afford compound **29** (67 mg, 64%) as a white solid. The relative stereochemistry of **29** was confirmed by X-ray crystallographic analysis.⁴



$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 9.11 (t, 1H, $J = 2.0$ Hz, Ar-H), 8.69 (d, 2H, $J = 2.0$ Hz, 2Ar-), 4.47 (t, 1H, $J = 7.9$ Hz, H-6), 3.76 (m, 1H, H-4 α), 3.38 (m, 1H, H-4 β), 2.62 (t, 1H, $J = 8.9$ Hz, H-2), 2.31-2.17 (m, 2H, H-7 α and H-3 α), 2.04 (m, 2H, H-3 β and H-10 α), 1.82 (m, 1H, H-7 β), 1.70 (m, 2H, H-10 β and H-11 α), 1.61 (m, 2H, 2H-9), 1.36 (d, 1H, $J_{11\alpha,11\beta} = 10.8$ Hz, H-11 β), 1.08 (s, 3H, CH_3).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 166.4 (C=O), 148.6 (2C, Ar-C), 140.8 (Ar-C), 127.8 (2C, Ar-C), 120.3 (Ar-C), 80.1 (C-1), 58.0 (C-6), 52.3 (C-11), 51.6 (C-4), 49.0 (C-2), 43.4 (C-7), 39.1 (C-8), 34.3 (C-10), 34.0 (C-9), 28.1 (CH_3), 26.9 (C-3).

FTIR (KBr) ν_{max} : 3435, 2945, 1627, 1541, 1344, 1075, 729 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{18}\text{H}_{22}\text{N}_3\text{O}_6$ [$\text{M}+\text{H}$] $^+$: 376.1503, found: 376.1515

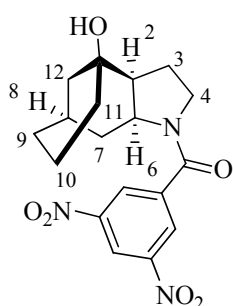
Mp: 192-194 $^\circ\text{C}$

Synthesis of *rac*-(3,5-dinitrophenyl)[(1*S*,2*S*,6*S*,8*R*)-1-hydroxy-5-azatetracyclo[6.3.1.0^{2,6}]dodecan-5-yl]methanone (30).

Sodium borohydride (21 mg, 0.56 mmol) was added to a solution of compound **25** (50 mg, 0.28 mmol) in absolute ethanol (5 mL) at 0°C . After 45 minutes the reaction mixture was quenched with saturated NH_4Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH_2Cl_2 (3 X 30 mL). The combined organic phases were dried over MgSO_4 , filtered, and concentrated in vacuo. The crude material was dissolved in CH_2Cl_2 (10 mL) and cooled to 0°C . Et_3N (76 μL , 0.56 mmol) and 3,5-dinitrobenzoyl chloride (97 mg, 0.42 mmol) were sequentially added. After stirring at room temperature for 8 hours the reaction mixture was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO_4 , filtered and concentrated in

⁴ Los datos de difracción de rayos X del compuesto **29** se encuentran en el anexo II.

vacuo. The crude solid was purified by chromatography (silica gel, gradient from 8:2 to 3:7 hexanes/EtOAc) to afford compound **30** (60 mg, 57%) as a white solid.



¹H-NMR (300 MHz, CDCl₃): δ 9.04 (t, 1H, J = 2.1 Hz, Ar-H), 8.63 (s, 2H, Ar-H), 4.41 (m, 1H, H-6), 3.56 (m, 1H, H-4 α), 3.31 (m, 1H, H-4 β), 2.44 (m, 1H, H-2), 2.37 (m, 1H, H-3 α), 2.30 (m, 1H, H-7 α), 2.13 (m, 1H, H-8), 1.92 (m, 1H, H-3 β), 1.86 (m, 1H, H-7 β), 1.77-1.59 (m, 4H, 2H-11, H-10 α and H-12 α), 1.50-1.30 (m, 4H, H-12 β , H-10 β and 2H-9).

¹³C-NMR (75 MHz, CDCl₃): δ 165.7 (C=O), 148.2 (2C, Ar-C), 140.5 (Ar-C), 127.6 (2C, Ar-C), 119.9 (Ar-C), 70.3 (C-1), 57.2 (C-6), 50.8 (C-2), 49.0 (C-4), 42.2 (C-12), 35.8 (C-7), 31.4 (C-11), 30.1 (C-8), 29.7 (C-9), 25.8 (C-3), 20.1 (C-10).

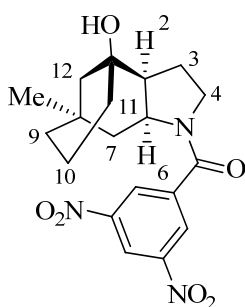
FTIR (KBr) ν_{max} : 3430, 2942, 1624, 1539, 1340 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₈H₂₂N₃O₆ [M+H]⁺: 376.1515, found: 376.1516

Mp: 195-198°C

Synthesis of *rac*-(3,5-dinitrophenyl)[(1*S*,2*S*,6*S*,8*R*)-1-hydroxy-8-methyl-5-azatetracyclo[6.3.1.0^{2,6}]dodecan-5-yl]methanone (31**).**

Sodium borohydride (19 mg, 0.52 mmol) was added to a solution of compound **26** (50 mg, 0.26 mmol) in absolute ethanol (5 mL) at 0°C. After 45 minutes the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 X 30 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated in vacuo. The crude material was dissolved in CH₂Cl₂ (10 mL) and cooled to 0°C. Et₃N (72 μ L, 0.52 mmol) and 3,5-dinitrobenzoyl chloride (90 mg, 0.39 mmol) were sequentially added. After stirring at room temperature for 8 hours the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from 8:2 to 3:7 hexanes/EtOAc) to afford compound **31** (74 mg, 73%) as a white solid.



¹H-NMR (400 MHz, CDCl₃): δ 9.16 (s, 1H, Ar-H), 8.75 (d, 2H, *J* = 2.0 Hz, H, Ar-H), 4.49 (dt, 1H, *J* = 8.7, 3.6 Hz, H-6), 3.68 (m, 1H, H-4 α), 3.36 (m, 1H, H-4 β), 2.46 (m, 1H, H-2), 2.19 (m, 1H, H-7 α), 1.98 (m, 2H, H-3 α and H-7 β), 1.90 (m, 1H, H-3 β), 1.81 (m, 2H, H-11 α and H-12 α), 1.67 (m, 1H, H-11 β), 1.51 (m, 1H, H-9 α), 1.41 (m, 1H, H-12 β), 1.33 (m, 1H, H-10 α), 1.29 (m, 1H, H-9 β), 1.16 (m, 1H, H-10 β), 1.02 (s, 3H, CH₃).

¹³C-NMR (100 MHz, CDCl₃): δ 165.7 (C=O), 148.4 (2C, Ar-C), 140.5 (Ar-C), 127.6 (2C, Ar-C), 120.0 (Ar-C), 71.7 (C-1), 57.7 (C-6), 50.8 (C-2), 49.8 (C-4), 48.4 (C-12), 39.0 (C-7), 37.3 (C-11), 35.0 (C-8), 34.4 (C-9), 32.3 (CH₃), 25.9 (C-3), 20.9 (C-10).

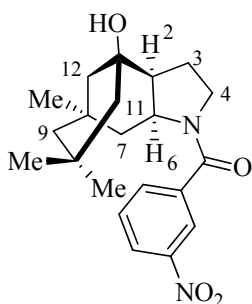
FTIR (KBr) ν_{\max} : 3432, 2944, 1625, 1542, 1341 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₉H₂₄N₃O₆ [M+H]⁺: 390.1665, found: 390.1664

Mp: 105-107°C

Synthesis of *rac*-(3-nitrophenyl)[(1*S*,2*S*,6*S*,8*R*)-1-hydroxy-8,10,10-trimethyl-5-azatetracyclo[6.3.1.0^{2,6}]dodecan-5-yl]methanone (32).

Sodium borohydride (17 mg, 0.46 mmol) was added to a solution of compound **27** (50 mg, 0.23 mmol) in absolute ethanol (10 mL) at 0°C. After 45 minutes the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 X 30 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated in vacuo. The crude material was dissolved in CH₂Cl₂ (10 mL) and cooled to 0°C. Et₃N (64 μ L, 0.46 mmol) and 3-nitrobenzoyl chloride (65 mg, 0.35 mmol) were sequentially added. After stirring at room temperature for 8 hours the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from 8:2 to 3:7 hexanes/EtOAc) to afford compound **32** (33 mg, 40%) as a white solid.



¹H-NMR (400 MHz, CDCl₃): δ 8.31 (t, 1H, *J* = 1.7 Hz, Ar-H), 8.27 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.80 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.60 (t, 1H, *J* = 8.0 Hz, Ar-H), 4.54 (m, 1H, H-6), 3.61 (m, 1H, H-4 α), 3.40 (m, 1H, H-4 β), 2.49 (m, 1H, H-2), 2.06-1.97 (m, 3H, 2H-3 and H-7 α), 1.89 (d, 1H, *J*_{11 α ,11 β} = 15.3 Hz, H-11 α), 1.69 (d, 1H, *J*_{12 α ,12 β} = 12.3 Hz, H-12 α), 1.53-1.36 (m, 4H, H-7 β , H-9 α , H-11 β and H-12 β), 1.28-1.19 (m, 1H, H-9 β),

1.13 (s, 3H, CH₃), 1.07 (s, 3H, CH₃), 1.05 (s, 3H, CH₃).

¹³C-NMR (100 MHz, CDCl₃): δ 167.1 (C=O), 147.8 (Ar-C), 138.7 (Ar-C), 133.2 (Ar-C), 129.6 (Ar-C), 124.6 (Ar-C), 122.2 (Ar-C), 73.1 (C-1), 56.2 (C-6), 51.2 (C-2), 50.9 (C-9), 49.7 (C-4), 46.6 (C-11), 44.9 (C-12), 38.2 (C-7), 35.3 (CH₃), 34.6 (CH₃), 31.7 (CH₃), 31.5 (C-8), 31.1 (C-10), 25.3 (C-3).

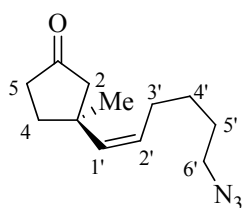
FTIR (KBr) v_{max}: 3435, 2950, 1625, 1533, 1441, 1350 cm⁻¹.

HRMS-ESI (m/z): calcd for C₂₁H₂₉N₂O₄ [M+H]⁺: 373.2133, found: 373.2123

Mp: 51-54°C

Wittig reaction. Synthesis of (Z)-3-(6-azidohex-1-en-1-yl)-3-methylcyclopentanone (**33**).

Phosphonium salt **6** (1.08 g, 2.38 mmol) was dissolved in dry CH₂Cl₂ (3 mL). THF (27 mL) was added and the mixture was cooled to -78°C. Then KHMDS (4.76 mL, 2.38 mmol, 0.5 M solution in toluene) was added. After the reaction mixture was stirred for 30 minutes at -78°C, a solution of aldehyde **13** (200 mg, 1.58 mmol) in dry THF (20 mL) was added dropwise over 20 minutes. After 1 hour the reaction mixture was warmed to room temperature over 1 hour. The reaction was quenched with saturated NH₄Cl solution and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) provided compound **33** (227 mg, 65 %) as a colorless oil.



¹H-NMR (300 MHz, CDCl₃): δ 5.49 (dt, 1H, *J*_{1',2'} = 11.6, *J*_{1',3'} = 1.7 Hz, H-1'), 5.28 (dt, 1H, *J*_{2',1'} = 11.6, *J*_{2',3'} = 7.4 Hz, H-2'), 3.28 (t, 2H, *J*_{6',5'} = 6.7 Hz, 2H-6'), 2.41-2.21 (m, 4H, 2H-2 and 2H-4), 2.16 (m, 2H, 2H-3'), 2.05 (m, 1H, H-5α), 1.95 (m, 1H, H-5β), 1.61 (m, 2H, 2H-5'), 1.46 (m, 2H, 2H-4'), 1.23 (s, 3H, CH₃).

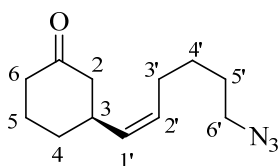
¹³C-NMR (75 MHz, CDCl₃): δ 219.4 (C=O), 137.4 (C-1'), 130.6 (C-2'), 53.2 (C-2), 51.5 (C-6'), 41.1 (C-3), 37.5 (C-5), 36.7 (C-4), 28.7 (C-5'), 28.4 (C-3'), 27.2 (C-4'), 26.8 (CH₃).

FTIR (neat) v_{max}: 3369, 2955, 2097, 1743, 1250, 1168 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₂H₁₉N₃NaO [M+Na]⁺: 244.1420, found: 244.1423

Wittig reaction. Synthesis of (Z)-3-(6-azidohex-1-en-1-yl)cyclohexanone (34).

Phosphonium salt **6** (2.15 g, 4.78 mmol) was dissolved in dry CH_2Cl_2 (3 mL). THF (27 mL) was added and the mixture was cooled to -78°C . Then KHMDS (9.56 mL, 4.78 mmol, 0.5 M solution in toluene) was added. After the reaction mixture was stirred for 30 minutes at -78°C , a solution of aldehyde **16** (400 mg, 3.17 mmol) in dry THF (20 mL) was added dropwise over 20 minutes. After 50 minutes, the reaction mixture was warmed to room temperature over 1 hour. The reaction was quenched with saturated NH_4Cl solution and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) provided compound **34** as a colorless oil (567 mg, 81%).



$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 5.27 (m, 2H, H-1' and H-2'), 3.23 (t, 2H, $J_{6',5'} = 6.7$ Hz, 2H-6'), 2.72 (m, 1H, H-3), 2.28 (m, 3H, H-2 α and 2H-6), 2.16-1.98 (m, 4H, H-2 β , 2H-3' and H-4 α), 1.81-1.64 (m, 2H, 2H-5), 1.56 (m, 2H, 2H-5'), 1.49-1.35 (m, 3H, 2H-4' and H-4 β).

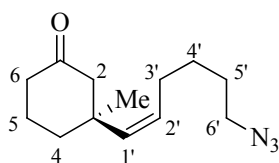
$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 21.1 (C=O), 133.2 (C-1'), 129.1 (C-2'), 51.3 (C-6'), 48.0 (C-2), 41.2 (C-6), 37.5 (C-3), 31.8 (C-4), 28.5 (C-5'), 26.9 (C-3'), 26.8 (C-4'), 25.4 (C-5).

FTIR (neat) ν_{max} : 3401, 2937, 2097, 1713 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{12}\text{H}_{19}\text{N}_3\text{NaO}$ $[\text{M}+\text{Na}]^+$: 244.1420, found: 244.1422

Wittig reaction. Synthesis of (Z)-3-(6-azidohex-1-en-1-yl)-3-methylcyclohexanone (35).

Phosphonium salt **6** (1.46 g, 3.23 mmol) was dissolved in dry CH_2Cl_2 (3 mL). THF (27 mL) was added and the mixture was cooled to -78°C . Then KHMDS (6.46 mL, 3.23 mmol, 0.5 M solution in toluene) was added. After the reaction mixture was stirred for 30 minutes at -78°C , a solution of aldehyde **19** (300 mg, 2.14 mmol) in dry THF (25 mL) was added dropwise over 20 minutes. After 50 minutes, the reaction mixture was warmed to room temperature over 1 hour. The reaction was quenched with saturated NH_4Cl solution and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) provided compound **35** as a colorless oil (327 mg, 65%).



$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 5.22 (m, 2H, H-1' and H-2'), 3.26 (t, 2H, $J_{6',5'} = 6.8$ Hz, 2H-6'), 2.48 (d, 1H, $J_{2\alpha,2\beta} = 13.4$ Hz, H-2 α), 2.29-2.13 (m, 5H, H-2 β , 2H-6 and 2H-3'), 1.87 (m, 3H, 2H-5 and H-4 α), 1.61 (m, 3H, 2H-5' and H-4 β), 1.44 (m, 2H, 2H-4'), 1.16 (s, 3H, CH_3).

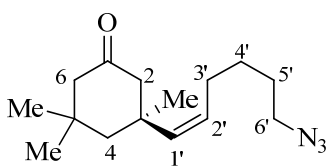
$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 211.4 (C=O), 136.1 (C-1'), 130.9 (C-2'), 54.8 (C-2), 51.4 (C-6'), 41.3 (C-3), 40.9 (C-6), 38.0 (C-4), 28.6 (2C, C-3' and C-5'), 28.2 (CH_3), 27.1 (C-4'), 22.6 (C-5).

FTIR (neat) ν_{max} : 3371, 2957, 2099, 1745, 1252 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{13}\text{H}_{22}\text{NO}$ $[\text{M}+\text{H}-\text{N}_2]^+$: 208.1819, found: 208.1823

Wittig reaction. Synthesis of (Z)-3-(6-azidohex-1-en-1-yl)-3,5,5-trimethylcyclohexanone (36).

Phosphonium salt **6** (1.08 g, 2.38 mmol) was dissolved in CH_2Cl_2 (2 mL). THF (18 mL) was added and the mixture was cooled to -78°C . Then KHMDS (4.76 mL, 2.38 mmol, 0.5 M solution in toluene) was added. After the reaction mixture was stirred for 30 minutes at -78°C , a solution of aldehyde **22** (200 mg, 1.19 mmol) in dry THF (20 mL) was added dropwise over 20 minutes. After 50 minutes, the reaction mixture was warmed to room temperature over 1 hour. The reaction was quenched with saturated NH_4Cl solution and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) afforded compound **36** (231 mg, 74%) as a colorless oil.



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.33 (d, 1H, $J_{1',2'} = 12.0$ Hz, H-1'), 5.12 (dt, 1H, $J_{2',1'} = 12.0$, $J_{2',3'} = 7.0$ Hz, H-2'), 3.26 (t, 2H, $J_{6',5'} = 6.8$ Hz, 2H-6'), 2.48 (d, 1H, $J_{2\alpha,2\beta} = 13.4$ Hz, H-2 α), 2.28-2.06 (m, 5H, 2H-3', 2H-6 and H-2 β), 1.93 (d, 1H, $J_{4\alpha,4\beta} = 14.0$ Hz, H-4 α), 1.60 (m, 3H, 2H-5' and H-4 β), 1.43 (m, 2H, 2H-4'), 1.20 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 0.95 (s, 3H, CH_3).

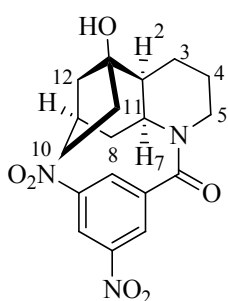
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 211.6 (C=O), 137.2 (C-1'), 129.7 (C-2'), 54.4 (C-6), 54.0 (C-2), 51.4 (C-6'), 51.1 (C-4), 40.9 (C-3), 36.4 (C-5), 32.9 (CH_3), 31.2 (CH_3), 29.3 (CH_3), 28.6 (C-5'), 28.3 (C-3'), 26.9 (C-4').

FTIR (neat) ν_{max} : 3400, 2956, 2097, 1714, 1458, 1280 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{15}\text{H}_{26}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 264.2070, found: 264.2070

Cyclization of 8. Synthesis of *rac*-(3,5-dinitrophenyl)[(1*S*,2*S*,7*S*,9*R*)-1-hydroxy-6-azatetracyclo[7.2.1.0^{2,7}]dodecan-6-yl]methanone (37).

A solution of compound **8** (100 mg, 0.48 mmol) in DMF (8 mL) was heated in a microwave reactor at 120°C for 3 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The resulting reaction crude was then passed through a plug of neutral alumina (2% methanol in dichloromethane) to remove the nonpolar impurities and afforded imino alcohol **9** as a viscous yellow oil. The crude material was dissolved in absolute ethanol (6 mL), cooled to 0°C and sodium borohydride (36 mg, 0.96 mmol) was added. After 45 minutes the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 X 30 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated in vacuo. The crude oil was dissolved in CH₂Cl₂ (5 mL), cooled to 0°C and Et₃N (0.133 mL, 0.96 mmol) and 3,5-dinitrobenzoyl chloride (163 mg, 0.71 mmol) were added sequentially. After stirring at room temperature for 8 hours the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from 7:3 to 3:7 hexanes/EtOAc) to afford compound **37** (92 mg, 51% from **8**, 3 steps) as a white solid.



¹H-NMR [500 MHz, CDCl₃, mixture of two conformers (2 : 1), major conformer]: δ 9.06 (s, 1H, Ar-H), 8.51 (s, 2H, Ar-H), 5.06 (dt, 1H, *J*_{7,2} = 12.3, *J* = 7.4 Hz, H-7), 3.39 (d, 1H, *J*_{5α,5β} = 13.4 Hz, H-5α), 3.05 (m, 1H, H-5β), 2.39 (m, 1H, H-2), 2.38 (m, 3H, H-3α, H-8α and H-12α), 2.11 (m, 1H, H-11α), 2.00 (m, 2H, H-4α and H-10α), 1.77 (m, 1H, H-9), 1.43 (m, 4H, H-3β, H-4β, H-8β and H-10β), 1.27 (m, 2H, H-11β and H-12β).

¹³C-NMR [500 MHz, CDCl₃, mixture of two conformers (2 : 1), major conformer]: δ 165.6 (C=O), 148.5 (2C, Ar-C), 140.1 (Ar-C), 127.1 (2C, Ar-C), 119.3 (Ar-C), 80.2 (C-1), 46.3 (C-7), 45.5 (C-2), 44.2 (C-5), 38.2 (C-8), 33.1 (C-12), 32.6 (C-9), 30.9 (C-11), 30.3 (C-10), 25.7 (C-4), 23.5 (C-3).

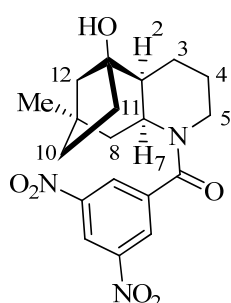
FTIR (KBr) ν_{max}: 3434, 3097, 2943, 2862, 1630, 1543, 1343 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₈H₂₂N₃O₆ [M+H]⁺: 376.1515, found: 376.1517

Mp: 183-185°C

Cyclization of 33. Synthesis of *rac*-(3,5-dinitrophenyl)[(1*S*,2*S*,7*S*,9*R*)-1-hydroxy-9-methyl-6-azatetracyclo[7.2.1.0^{2,7}]dodecan-6-yl]methanone (38).

A solution of compound **33** (100 mg, 0.45 mmol) in DMF (8 mL) was heated in a microwave reactor at 120°C for 3 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The resulting reaction crude was then passed through a plug of neutral alumina (2% methanol in dichloromethane) to remove the nonpolar impurities and afforded imino alcohol as a viscous yellow oil. The crude material was dissolved in absolute ethanol (6 mL), cooled to 0°C and sodium borohydride (34 mg, 0.9 mmol) was added. After 45 minutes the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 X 30 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated in vacuo. The crude oil was dissolved in CH₂Cl₂ (5 mL), cooled to 0°C and Et₃N (0.125 mL, 0.90 mmol) and 3,5-dinitrobenzoyl chloride (154 mg, 0.67 mmol) were added sequentially. After stirring at room temperature for 8 hours the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from 7:3 to 3:7 hexanes/EtOAc) to afford compound **38** (94 mg, 54% from **33**, 3 steps) as a white solid.



¹H-NMR [400 MHz, CDCl₃, mixture of two conformers (2 : 1), major conformer]: δ 9.06 (m, 1H, Ar-H), 8.51 (s, 2H, Ar-H), 5.06 (m, 1H, H-7), 3.39 (d, 1H, *J*_{5α,5β} = 12.8 Hz, H-5α), 3.04 (m, 1H, H-5β), 2.16-1.95 (m, 4H, H-2, H-3α, H-12α and H-11α), 1.95-1.68 (m, 3H, H-4α, H-8α and H-10α), 1.59-1.36 (m, 4H, H-3β, H-4β and H-10β, H-8β), 1.35-1.27 (m, 2H, H-11β and H-12β), 1.18 (s, 3H, CH₃).

¹³C-NMR [100 MHz, CDCl₃, mixture of two conformers (2 : 1), major conformer]: δ 165.7 (C=O), 148.6 (2C, Ar-C), 140.3 (Ar-C), 127.2 (2C, Ar-C), 119.4 (Ar-C), 80.5 (C-1), 46.9 (C-7), 45.8 (C-12), 44.7 (C-2), 44.4 (C-5), 40.2 (C-10), 38.4 (C-8), 37.6 (C-9), 34.2 (C-11), 29.1 (CH₃), 25.8 (C-4), 23.6 (C-3).

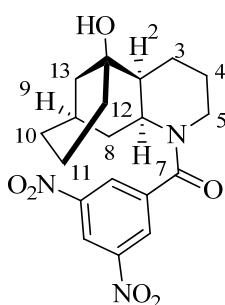
FTIR (KBr) ν_{max}: 3436, 3099, 2944, 2863, 1629, 1544, 1344, 1279, 1067, 730 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₉H₂₄N₃O₆ [M+H]⁺: 390.1662, found: 390.1662

Mp: 72-75°C

Cyclization of 34. Synthesis of *rac*-(3,5-dinitrophenyl)[(1*S*,2*S*,7*S*,9*R*)-1-hydroxy-6-azatetracyclo[7.3.1.0^{2,7}]tridecan-6-yl]methanone (39).

A solution of compound **34** (100 mg, 0.45 mmol) in DMF (8 mL) was heated in a microwave reactor at 120°C for 3 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The resulting reaction crude was then passed through a plug of neutral alumina (2% methanol in dichloromethane) to remove the nonpolar impurities and afforded imino alcohol as a viscous yellow oil. The crude material was dissolved in absolute ethanol (6 mL), cooled to 0°C and sodium borohydride (34 mg, 0.9 mmol) was added. After 45 minutes the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 X 30 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated in vacuo. The crude oil was dissolved in CH₂Cl₂ (5 mL), cooled to 0°C and Et₃N (0.125 mL, 0.90 mmol) and 3,5-dinitrobenzoyl chloride (154 mg, 0.67 mmol) were added sequentially. After stirring at room temperature for 8 hours the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from 7:3 to 3:7 hexanes/EtOAc) to afford compound **39** (94 mg, 54% from **34**, 3 steps) as a white solid.



¹H-NMR [400 MHz, CDCl₃, mixture of two conformers (2.5 : 1), major conformer]: δ 9.06 (t, 1H, *J* = 2.1 Hz, Ar-H), 8.52 (d, 2H, *J* = 2.1 Hz, Ar-H), 5.06 (m, 1H, H-7), 3.40 (d, 1H, *J*_{5α,5β} = 13.0 Hz, H-5α), 3.04 (dt, 1H, *J*_{5β,5α} = 13.0, 1.9 Hz, H-5β), 2.45 (m, 1H, H-2), 2.17 (m, 2H, H-3α, H-13α), 1.95 (m, 3H, H-4α, H-8α and H-12α), 1.72 (m, 4H, H-4β, H-8β, H-13β and H-3β), 1.57-1.15 (m, 6H, H-9, 2H-10, 2H-11 and H-12β).

¹³C-NMR [400 MHz, CDCl₃, mixture of two conformers (2 : 1), major conformer]: δ 165.6 (C=O), 148.7 (2C, Ar-C), 140.5 (Ar-C), 127.3 (2C, Ar-C), 119.5 (Ar-C), 72.4 (C-1), 47.5 (C-7), 45.1 (C-2), 44.5 (C-5), 38.8 (C-8), 37.0 (C-13), 31.2 (C-12), 27.4 (C-10), 26.0 (C-4), 23.9 (C-3), 21.2 (C-9), 19.8 (C-11).

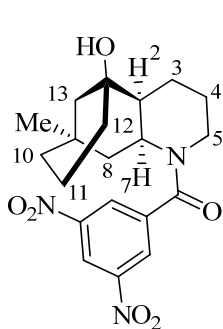
FTIR (KBr) ν_{max}: 3421, 2948, 2870, 1619, 1548, 1340 cm⁻¹

HRMS-ESI (m/z): calcd for C₁₉H₂₄N₃O₆ [M+H]⁺: 390.1662, found: 390.1664

Mp: 220-222°C

Cyclization of 35. Synthesis of *rac*-(3,5-dinitrophenyl)[(1*S*,2*S*,7*S*,9*R*)-1-hydroxy-9-methyl-6-azatetracyclo[7.3.1.0^{2,7}]tridecan-6-yl]methanone (40).

A solution of compound **35** (100 mg, 0.42 mmol) in DMF (8 mL) was heated in a microwave reactor at 120 °C for 3 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The resulting reaction crude was then passed through a plug of neutral alumina (2% methanol in dichloromethane) to remove the nonpolar impurities and afforded imino alcohol as a viscous oil. The crude material was dissolved in absolute ethanol (6 mL), cooled to 0°C and sodium borohydride (32 mg, 0.84 mmol) was added. After 45 minutes the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 X 30 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated in vacuo. The crude oil was dissolved in CH₂Cl₂ (5 mL), cooled to 0°C and Et₃N (0.116 mL, 0.84 mmol) and 3,5-dinitrobenzoyl chloride (145 mg, 0.63 mmol) were added sequentially. After stirring at room temperature for 8 hours the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from 7:3 to 3:7 hexanes/EtOAc) to afford compound **40** (96 mg, 57% from **35**, 3 steps) as a white solid.



¹H-NMR [500 MHz, CDCl₃, mixture of two conformers (2:1), major conformer]: δ 9.10 (d, 1H, *J* = 2.0 Hz, Ar-H), 8.64 (d, 2H, *J* = 2.0 Hz, Ar-H), 5.06 (m, 1H, H-7), 3.39 (d, 1H, *J*_{5α,5β} = 13.1 Hz, H-5α), 3.04 (t, 1H, *J*_{5β,5α} = 13.1 Hz, H-5β), 2.42 (m, 1H, H-2), 2.14-1.96 (m, 2H, H-3α and H-13α), 1.95-1.71 (m, 3H, H-4α, H-8α and H-12α), 1.52 (m, 4H, H-3β, H-4β, H-8β and H-13β), 1.38-1.25 (m, 5H, 2H-10, 2H-11 and H-12β), 1.17 (s, 3H, CH₃).

¹³C-NMR [125 MHz, CDCl₃, mixture of two conformers (2 : 1), major conformer]: δ 165.4 (C=O), 148.5 (2C, Ar-C), 140.2 (Ar-C), 127.1 (2C, Ar-C), 119.6 (Ar-C), 71.8 (C-1), 48.5 (C-7), 45.2 (C-2), 44.5 (C-5), 39.2 (C-13), 38.6 (C-8), 34.2 (C-12), 30.3 (C-9), 29.9 (CH₃), 27.6 (C-10), 25.9 (C-4), 23.7 (C-3), 19.9 (C-11).

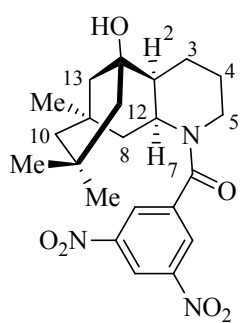
FTIR (KBr) ν_{max}: 3435, 3098, 2954, 2861, 1630, 1543, 1343 cm⁻¹.

HRMS-ESI (m/z): calcd for C₂₀H₂₆N₃O₆ [M+H]⁺: 404.1822, found: 404.1824

Mp: 247-249°C

Cyclization of 36. Synthesis of *rac*-(3,5-dinitrophenyl)[(1*S*,2*S*,7*S*,9*R*)-1-hydroxy-9,11,11-trimethyl-6-azatetracyclo[7.3.1.0^{2,7}]tridecan-6-yl]methanone (41).

A solution of compound **36** (100 mg, 0.38 mmol) in DMF (8 mL) was heated in a microwave reactor at 120°C for 12 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The resulting reaction crude was then passed through a plug of neutral alumina (2% methanol in dichloromethane) to remove the nonpolar impurities and afforded imino alcohol as a viscous oil. The crude material was dissolved in absolute ethanol (6 mL), cooled to 0°C and sodium borohydride (29 mg, 0.76 mmol) was added. After 45 minutes the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 X 30 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated in vacuo. The crude oil was dissolved in CH₂Cl₂ (5 mL), cooled to 0°C and Et₃N (0.105 mL, 0.76 mmol) and 3,5-dinitrobenzoyl chloride (131 mg, 0.57 mmol) were added sequentially. After stirring at room temperature for 8 hours the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) to afford compound **41** (25 mg, 15% from **36**, 3 steps) as a white solid.



¹H-NMR [400 MHz, CDCl₃, mixture of two conformers (2 : 1), major conformer]: δ 9.07 (s, 1H, Ar-H), 8.51 (d, 2H, *J* = 1.7 Hz, Ar-H), 4.93 (m, 1H, H-7), 3.41 (d, 1H, *J*_{5α,5β} = 13.2 Hz, H-5α), 3.00 (t, 1H, *J* = 12.2 Hz, H-5β), 2.13-1.92 (m, 3H, H-2, H-3α and H-12α), 1.88-1.62 (m, 4H, H-3β, H-8α, H-4α and H-13α), 1.52-1.35 (m, 3H, H-4β, H-8β and H-10α), 1.34-1.22 (m, 3H, H-10β, H-12β and H-13β), 1.19 (s, 3H, CH₃), 1.11 (s, 3H, CH₃), 1.09 (s, 3H, CH₃).

¹³C-NMR [100 MHz, CDCl₃, mixture of two conformers (2 : 1), major conformer]: δ 165.7 (C=O), 148.9 (2C, Ar-C), 140.7 (Ar-C), 127.5 (2C, Ar-C), 119.7 (Ar-C), 74.9 (C-1), 52.5 (C-10), 49.0 (C-12), 47.5 (C-7), 45.5 (2C, C-2 and C-5), 44.4 (C-13), 37.7 (CH₃), 35.0 (CH₃), 34.1 (C-8), 32.5 (C-11), 32.2 (CH₃), 31.9 (C-9), 25.8 (C-4), 22.9 (C-3).

FTIR (KBr) ν_{max}: 3419, 2949, 2868, 1616, 1545, 1344, 727 cm⁻¹.

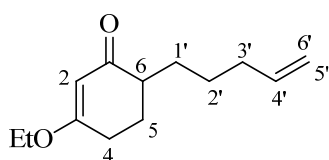
HRMS-ESI (m/z): calcd for C₂₂H₃₀N₃O₆ [M+H]⁺: 432.2129, found: 432.2142

Mp: 215-218°C

2.3.2.2.- Synthesis of tetracyclic imino alcohols.

Synthesis of 3-ethoxy-6-(pent-4-en-1-yl)cyclohex-2-enone (**42**).

To a stirred -78°C solution of freshly prepared LDA (10.26 mmol) in 30 mL of THF was added dropwise via cannula a solution of 3-ethoxy-2-cyclohexen-1-one (1.29 g, 10.24 mmol) in 20 mL of THF. After stirring the mixture at -78°C for 30 minutes, a solution of 4-pentenyl iodide⁵ (2.00 g, 10.24 mmol) in 20 mL of THF was added dropwise via cannula to the enolate solution. The reaction flask was then removed from the dry ice/acetone bath and warmed to 23°C . Stirring was continued at this temperature for 5 hours before 50 mL of saturated aqueous NH_4Cl was slowly added to quench the reaction. The solution was transferred to a separatory funnel and extracted with EtOAc (2 X 75 mL). The combined organic extracts were washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 6:4 hexanes/EtOAc) afforded compound **42** (1.34 g, 63%) as a pale yellow liquid, which had spectroscopic data identical to those of the previously reported.⁶



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.77 (m, 1H, H-4'), 5.27 (s, 1H, H-2), 4.96 (m, 2H, H-5' y H-6'), 3.85 (q, 2H, $J = 7.1$ Hz, $\text{CH}_3\text{CH}_2\text{O}$), 2.39 (m, 2H, H-6 and H-4 α), 2.22-1.89 (m, 7H, H-4 β , 2H-1', 2H-2' and 2H-3'), 1.69 (m, 1H, H-5 α), 1.41 (m, 1H, H-5 β) 1.32 (t, 3H, $J = 7.1$ Hz, $\text{CH}_3\text{CH}_2\text{O}$).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 201.6 (C=O), 176.8 (C-3), 138.4 ($\text{CH}=\text{CH}_2$), 114.9 ($\text{CH}=\text{CH}_2$), 102.2 (C-2), 64.2 ($\text{CH}_3\text{CH}_2\text{O}$), 44.5 (C-6), 31.2 (C-3'), 28.7 (C-1'), 28.0 (C-4), 26.2 (C-2'), 14.2 (C-5), 13.3 ($\text{CH}_3\text{CH}_2\text{O}$).

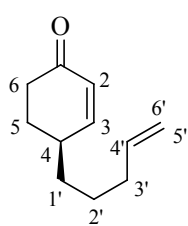
Synthesis of 4-(pent-4-en-1-yl)cyclohex-2-enone (**43**).

To an ice cold suspension of LiAlH_4 (164 mg, 4.32 mmol) in 150 mL of THF was added dropwise via cannula a solution of compound **42** (900 mg, 4.32 mmol) in 30 mL of Et_2O . Following the addition, the reaction flask was removed from the ice bath, warmed to 23°C and stirred for 2 ours. The mixture was then cooled to 0°C and 1 mL of H_2O was added dropwise over a 5 minutes period followed by the successive addition of 1 mL of 15% v/v aqueous NaOH , and 3 mL of H_2O . The resulting white suspension was stirred vigorously for 10 hours. The mixture was filtered through a small pad of Celite and the flask and filter cake were rinsed with 50 mL of EtOAc. The filtrate was concentrated under reduced pressure to afford a pale

⁵ J. Jin, M. Newcomb, *J. Org. Chem.* **2007**, 72, 5098-5103.

⁶ L. Meyer, P. Margaretha, *Photochem. Photobiol. Sci.* **2004**, 3, 684-688.

yellow oil. This material was dissolved in 30 mL of THF and to this solution was added slowly 8 mL of 5.0 M aqueous HCl. The pale yellow mixture was stirred at 23°C for 1 hour. The reaction contents were then diluted with 50 mL of H₂O and extracted with EtOAc (3 X 80 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) yielded compound **43** as a colorless oil (817 mg, 91%), which had spectroscopic data identical to those of the previously reported.⁷



¹H-NMR (300 MHz, CDCl₃): δ 6.85 (m, 1H, H-3), 5.97 (dd, 1H, $J_{2,3} = 10.3$, $J_{2,4} = 2.4$ Hz, H-2), 5.81 (m, 1H, H-4'), 5.06-4.96 (m, 2H, H-5' and H-6'), 2.55-2.27 (m, 2H, H-4 and H-6 α), 2.16-2.07 (m, 2H, H-6 β and H-3' α), 1.75-1.62 (m, 1H, H-5 α), 1.57-1.40 (m, 4H, H-1' α , H-2' α , H-5 β and H-3' β), 1.26-1.21 (m, 2H, H-2' β and H-1' β).

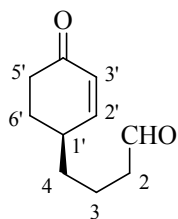
¹³C-NMR (75 MHz, CDCl₃): δ 199.9 (C=O), 155.0 (C-3), 138.2 (CH=CH₂), 128.9 (C-2), 114.8 (CH=CH₂), 36.9 (C-6), 35.9 (C-4), 33.9 (C-1'), 33.6 (C-3'), 28.5 (C-2'), 26.1 (C-5).

FTIR (neat) ν_{max} : 2927, 1683, 1459, 1252, 911 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₁H₁₇O [M+H]⁺: 165.1278, found: 165.1282

Ozonolysis of **43**. Synthesis of 4- (4-oxocyclohex-2-en-1-yl)butanal (**44**).

A solution of **43** (800 mg, 4.87 mmol) and Sudan red 7B (1 mg) in CH₂Cl₂ (60 mL) was ozonized at -78°C until the deep pink colour disappeared. Triphenylphosphine (2.54 g, 9.74 mmol) was added and the mixture was allowed to warm to room temperature overnight. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) to provide compound **44** as a colorless oil (712 mg, 88%).



¹H-NMR (300 MHz, CDCl₃): δ 9.72 (s, 1H, CHO), 6.78 (m, 1H, H-2'), 5.90 (d, 1H, $J_{3',2'} = 10.2$ Hz, H-3'), 2.50-2.21 (m, 5H, 2H-5', 2H-2 and H-1'), 2.06 (m, 1H, H-3 α), 1.67 (m, 3H, H-4 α , H-3 β and H-6' α), 1.45 (m, 2H, H-4 β and H-6' β).

¹³C-NMR (75 MHz, CDCl₃): δ 202.8 (CHO), 199.6 (C=O), 154.4 (C-2'), 129.1 (C-3'), 43.7 (C-2), 36.8 (C-5'), 35.9 (C-1'), 33.9 (C-4), 28.4 (C-6'), 19.3 (C-3).

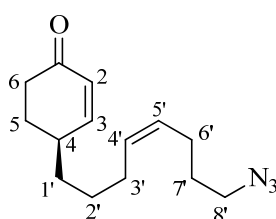
FTIR (neat) ν_{max} : 3416, 2938, 1723, 1669 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₀H₁₅O₂ [M+H]⁺: 167.1067, found: 167.1064

⁷ B. M. Trost, Z. T. Ball, T. Jöge, *J. Am. Chem. Soc.* **2002**, 27, 7922-7923.

Wittig reaction. Synthesis of (Z)-4-(8-azidoct-4-en-1-yl)cyclohex-2-enone (45).

To a solution of phosphonium salt **4** (1.57 g, 3.59 mmol) in dry THF (30 mL) was added KHMDS (7.18 mL, 3.59 mmol, 0.5 M solution in toluene) at -78°C . After the reaction mixture was stirred for 30 minutes at -78°C , a solution of aldehyde **44** (400 mg, 2.41 mmol) in dry THF (20 mL) was added dropwise over 20 minutes. After 50 minutes, the reaction mixture was warmed to room temperature over 1 hour. The reaction was quenched with saturated NH_4Cl solution and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) yielded compound **45** as a colorless oil (524 mg, 88%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 6.83 (m, 1H, H-3), 5.94 (dd, 1H, $J_{2,3} = 10.2$, $J_{2,4} = 2.5$ Hz, H-2), 5.36 (m, 2H, H-4' and H-5'), 3.25 (t, 2H, $J_{8',7'} = 6.8$ Hz, 2H-8'), 2.51-2.27 (m, 4H, 2H-6, H-4 and H-5 α), 2.08 (m, 5H, 2H-3', 2H-6' and H-5 β), 1.63 (m, 2H, 2H-7'), 1.44 (m, 4H, 2H-1' and 2H-2').

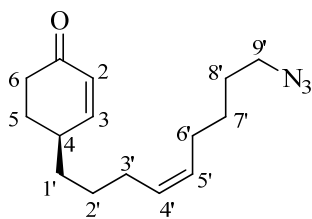
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 200.0 (C=O), 155.1 (C-3), 130.6 (C-4'), 129.4 (C-2), 129.0 (C-5'), 50.8 (C-8'), 37.0 (C-4), 36.1 (C-6), 34.2 (C-1'), 28.7 (2C, C-2' and C-7'), 27.2 (C-3'), 27.0 (C-6'), 24.3 (C-5).

FTIR (neat) ν_{max} : 3353, 2930, 2097, 1682 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{14}\text{H}_{22}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 248.1755, found: 248.1754

Wittig reaction. Synthesis of (Z)-4-(9-azidonon-4-en-1-yl)cyclohex-2-enone (46).

Phosphonium salt **6** (1.22 g, 2.72 mmol) was dissolved in dry CH_2Cl_2 (3 mL). THF (27 mL) was added and the solution was cooled to -78°C . Then KHMDS (5.44 mL, 2.72 mmol, 0.5 M solution in toluene) was added. After the reaction mixture was stirred for 30 minutes at -78°C , a solution of aldehyde **44** (300 mg, 1.81 mmol) in dry THF (20 mL) was added dropwise over 20 minutes. After 50 minutes, the reaction mixture was warmed to room temperature over 1 hour. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) provided compound **46** as a colorless oil (354 mg, 75%).



¹H-NMR (300 MHz, CDCl₃): δ 6.84 (m, 1H, H-3), 5.96 (dd, 1H, $J_{2,3} = 10.2$ Hz, $J_{2,4} = 2.4$ Hz, H-2), 5.37 (m, 2H, H-4' and H-5'), 3.26 (t, 2H, $J_{9',8'} = 6.8$ Hz, 2H-9'), 2.53-2.28 (m, 3H, 2H-6 and H-4), 2.07 (m, 5H, 2H-3', 2H-6' and H-5α), 1.74-1.53 (m, 3H, 2H-8' and H-5β), 1.45 (m, 6H, 2H-1', 2H-2' and 2H-7').

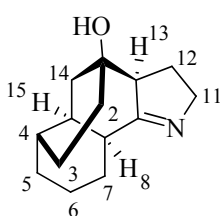
¹³C-NMR (75 MHz, CDCl₃): δ 199.9 (C=O), 155.0 (C-3), 129.7 (C-4'), 129.5 (C-2), 128.9 (C-5'), 51.3 (C-9'), 36.9 (C-4), 36.0 (C-6), 34.1 (C-1'), 28.5 (C-8'), 28.4 (C-2'), 27.1 (C-6'), 26.9 (C-3'), 26.7 (2C, C-5 and C-7').

FTIR (neat) ν_{\max} : 2932, 2096, 1681 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₅H₂₄N₃O [M+H]⁺: 262.1919, found: 262.1914

Cyclization of **45**. Synthesis of *rac*-(1*S*,4*S*,8*S*,13*S*,15*R*)-10-azatetracyclo[6.5.2.0^{4,15}.0^{9,13}]pentadec-9-en-1-ol (**47**).

DBU (0.18 mL, 1.20 mmol) was added to a solution of compound **45** (100 mg, 0.40 mmol) in DMF/ethanol (10 mL, 4:1). The mixture was heated in a microwave reactor at 120°C for 3 hours. The dark brown solution was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, gradient from CH₂Cl₂ to 97:3 CH₂Cl₂/MeOH) to afford the desired imino alcohol **47** (68 mg, 78%) as a pale yellow viscous oil.



¹H-NMR (400 MHz, CDCl₃): δ 4.00 (m, 1H, H-11α), 3.59 (m, 1H, H-11β), 2.74 (t, 1H, $J = 9.4$ Hz, H-13), 2.41 (m, 2H, H-8 and H-7α), 2.16 (m, 1H, H-12α), 2.08 (m, 1H, H-15), 1.95 (m, 1H, H-14α), 1.82 (m, 2H, H-2α and H-3α), 1.79-1.66 (m, 2H, H-4 and H-12β), 1.63-1.39 (m, 4H, H-2β, H-3β, H-7β and H-14β), 1.35-1.21 (m, 4H, 2H-5 and 2H-6).

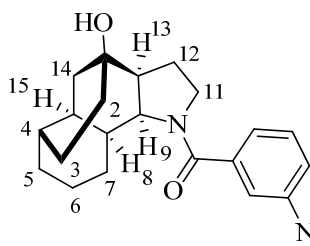
¹³C-NMR (100 MHz, CDCl₃): δ 179.9 (C=N), 71.2 (C-1), 59.1 (C-13), 58.7 (C-11), 44.8 (C-8), 38.7 (C-14), 38.5 (C-15), 35.0 (C-2), 34.7 (C-4), 30.7 (C-5), 26.5 (C-7), 24.3 (C-3), 23.2 (C-12), 15.7 (C-6).

FTIR (neat) ν_{\max} : 3330, 2950, 2860, 1649, 1460 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₄H₂₂NO [M+H]⁺: 220.1696, found: 220.1695

Synthesis of *rac*-(3-nitrophenyl)[(1*S*,4*S*,8*S*,9*S*,13*S*,15*R*)-1-hydroxy-10-azatetracyclo[6.5.2.0^{4,15}.0^{9,13}]pentadecan-3-yl]methanone (48).

Sodium borohydride (13 mg, 0.36 mmol) was added to a solution of compound **47** (40 mg, 0.18 mmol) in absolute ethanol (5 mL) at 0°C. After 45 minutes the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 X 30 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated in vacuo. The crude material was dissolved in CH₂Cl₂ (10 mL) and cooled to 0°C. Et₃N (50 µL, 0.36 mmol) and 3-nitrobenzoyl chloride (50 mg, 0.27 mmol) were sequentially added. After stirring at room temperature for 8 hours the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from 8:2 to 3:7 hexanes/EtOAc) to afford compound **48** (43 mg, 64%) as a white solid. The relative stereochemistry of **48** was confirmed by X-ray crystallographic.⁸



¹H-NMR (400 MHz, CDCl₃): δ 8.46 (m, 1H, Ar-H), 8.31 (m, 1H, Ar-H), 7.95 (m, 1H, Ar-H), 7.62 (m, 1H, Ar-H), 4.86 (t, 1H, *J* = 8.6 Hz, H-9), 3.64 (m, 1H, H-11α), 3.45 (m, 1H, H-11β), 2.59-2.43 (m, 2H, H-13 and H-7α), 2.38 (m, 1H, H-8), 2.10 (dd, 1H, *J* = 13.7, *J* = 6.1 Hz, H-12α), 1.98 (m, 1H, H-15), 1.88 (m, 2H, H-2α and H-3α), 1.77 (m, 2H, H-12β and H-4), 1.64 (m, 2H, 2H-14), 1.52 (m, 5H, 2H-5, H-6α, H-2β and H-3β), 1.36 (m, 1H, H-7β), 1.24 (m, 1H, H-6β).

¹³C-NMR (100 MHz, CDCl₃): δ 172.8 (C=O), 148.3 (Ar-C), 139.1 (Ar-C), 134.2 (Ar-C), 129.7 (Ar-C), 125.6 (Ar-C), 123.5 (Ar-C), 70.3 (C-1), 59.8 (C-9), 54.2 (C-11), 49.8 (C-13), 45.2 (C-14), 39.6 (C-15), 37.1 (C-8), 35.3 (C-2), 33.8 (C-4), 30.7 (C-5), 28.3 (C-7), 26.9 (C-12), 25.2 (C-3), 18.0 (C-6).

FTIR (KBr) ν_{max}: 3428, 2950, 1632, 1521, 1350 cm⁻¹.

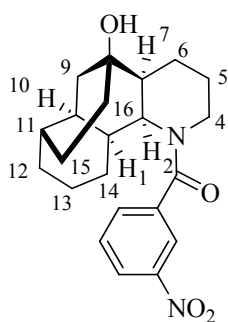
HRMS-ESI (m/z): calcd for C₂₁H₂₇N₂O₄ [M+H]⁺: 371.1968, found: 371.1964

Mp: 187-189°C

⁸ Los datos de difracción de rayos X del compuesto **48** se encuentran en el anexo II.

Synthesis of *rac*-(3-nitrophenyl)[(1*S*,2*S*,7*S*,8*S*,11*S*,15*R*)-8-hydroxy-3-azatetracyclo[6.6.2.0^{2,7}.0^{11,15}]hexadecan-3-yl]methanone (50).

A solution of compound **46** (100 mg, 0.38 mmol) in DMF (10 mL) was heated in a microwave reactor at 120°C for 3 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The resulting reaction crude was then passed through a plug of neutral alumina (2% methanol in dichloromethane) to remove the nonpolar impurities and afforded imino alcohol as a viscous oil. The crude material was dissolved in absolute ethanol (5 mL), cooled to 0°C and sodium borohydride (29 mg, 0.76 mmol) was added. After 50 minutes the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 X 30 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated in vacuo. The crude oil was dissolved in CH₂Cl₂ (5 mL), cooled to 0°C and Et₃N (0.105 ml, 0.76 mmol) and 3-nitrobenzoyl chloride (105 mg, 0.57 mmol) were sequentially added. After stirring at room temperature for 8 hours the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from 7:3 to 3:7 hexanes/EtOAc) to afford compound **50** (83 mg, 57% from **46**, 3 steps) as a white solid.



¹H-NMR [500 MHz, CDCl₃, mixture of two conformers (4 : 1), major conformer]:

δ 8.26 (m, 1H, Ar-H), 8.20 (m, 1H, Ar-H), 7.69 (m, 1H, Ar-H), 7.60 (t, 1H, *J* = 7.6 Hz, Ar-H), 5.25 (t, 1H, *J* = 8.6 Hz, H-2), 3.54 (m, 1H, H-4α), 3.12 (dt, 1H, *J* = 13.1, *J* = 2.5 Hz, H-4β), 2.83 (m, 1H, H-7), 2.33 (m, 2H, H-1 and H-14α), 2.26-2.16 (m, 1H, H-6α), 2.01 (m, 2H, H-10 and H-16α), 1.82-1.56 (m, 8H, H-15α, H-11, 2H-12, H-13α, H-5α, H-16β and H-9α), 1.48-1.22 (m, 6H, H-15β, H-14β, H-6β, H-13β, H-5β and H-9β)

¹³C-NMR [125 MHz, CDCl₃, mixture of two conformers (4 : 1), major conformer]:

δ 168.3 (C=O), 148.0 (Ar-C), 138.8 (Ar-C), 132.7 (Ar-C), 129.7 (Ar-C), 123.9 (Ar-C), 121.8 (Ar-C), 71.5 (C-8), 49.2 (C-2), 47.0 (C-4), 45.8 (C-7), 38.7 (C-9), 37.2 (C-10), 33.5 (C-1), 33.2 (C-16), 32.8 (C-11), 30.8 (C-12), 26.2 (C-14), 26.1 (C-5), 23.3 (C-6), 22.5 (C-15), 20.5 (C-13).

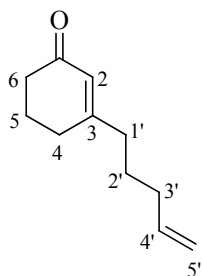
FTIR (KBr) ν_{max}: 3435, 2950, 1625, 1533, 1350 cm⁻¹.

HRMS-ESI (m/z): calcd for C₂₂H₂₉N₂O₄ [M+H]⁺: 385.2140, found: 385.2147

Mp: 178-180°C

Synthesis of 3-(pent-4-en-1-yl)cyclohex-2-enone (51).

A solution of 3-ethoxy-2-cyclohexenone (1.0 g, 7.13 mmol) in Et₂O (25 mL) was added dropwise to a freshly prepared Grignard reagent from 1-bromo-4-pentene (1.06 g, 7.13 mmol) and magnesium metal (225 mg, 9.27 mmol) in Et₂O (40 mL) at -78°C. After 30 minutes the solution was warmed to room temperature and stirred for an additional 2 hours. The reaction was then cooled to 0°C, 10% HCl (25 mL) was added, and the mixture was stirred for 30 minutes. The solution was diluted with 40 mL of brine and extracted with ether (3 X 40 mL). The combined extracts were washed (water, bicarbonate, and brine), dried over MgSO₄, filtered, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (gradient from hexanes to 4:1 hexanes/EtOAc) provided the desired product **51** as a colorless oil (585 mg, 50%).



¹H-NMR (300 MHz, CDCl₃): δ 5.86, (s, 1H, H-2), 5.77 (ddt, 1H, $J_{4',6'} = 17.2$, $J_{4',5'} = 10.3$, $J_{4',3'} = 6.7$ Hz, H-4'), 5.00 (m, 2H, H-5' and H-6'), 2.34 (t, 2H, $J_{6,5} = 6.9$ Hz, 2H-6), 2.27 (t, 2H, $J_{4,5} = 5.9$ Hz, 2H-4), 2.20 (t, 2H, $J_{1',2'} = 7.7$ Hz, 2H-1'), 2.06 (m, 2H, 2H-3'), 1.97 (m, 2H, 2H-5), 1.59 (m, 2H, 2H-2').

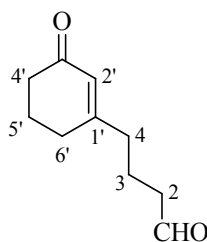
¹³C-NMR (75 MHz, CDCl₃): δ 200.0 (C=O), 166.4 (C-3), 138.0 (CH=CH₂), 125.9 (C-2), 115.4 (CH=CH₂), 37.5 (2C, C-1' and C-6), 33.3 (C-3'), 29.8 (C-4), 26.2 (C-2'), 22.8 (C-5).

FTIR (neat) ν_{max} : 3331, 2932, 1670, 1625, 1429, 1252 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₁H₁₇O [M+H]⁺: 165.1274, found: 165.1272

Ozonolysis of 51. Synthesis of 4-(3-oxocyclohex-1-en-1-yl)butanal (52)

A solution of compound **51** (400 mg, 2.43 mmol) and Sudan red 7B (1 mg) in CH₂Cl₂ (40 mL) was ozonized at -78°C until the deep pink colour disappeared. Triphenylphosphine (1.27 g, 4.86 mmol) was added and the mixture was allowed to warm to room temperature overnight. The solvent was removed and the crude product was purified by column chromatography on silica gel (gradient from hexanes to 7:3 hexanes/EtOAc) to afford compound **52** (375 mg, 93%) as a yellow oil.



¹H-NMR (300 MHz, CDCl₃): δ 9.75 (s, 1H, CHO), 5.84 (s, 1H, H-2'), 2.47 (t, 2H, $J_{2,3} = 7.1$ Hz, 2H-2), 2.33 (t, 2H, $J_{4',5'} = 6.6$ Hz, 2H-4'), 2.29-2.19 (m, 4H, 2-H6' and 2H-4), 1.96 (m, 2H, 2H-5'), 1.82 (m, 2H, 2H-3).

¹³C-NMR (75 MHz, CDCl₃): δ 201.5 (CHO), 199.8 (C=O), 165.1 (C-1'), 126.1 (C-2'), 43.1 (C-2), 37.4 (C-4'), 37.2 (C-4), 29.6 (C-6'), 22.7 (C-5'),

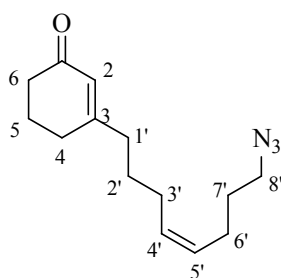
19.2 (C-3).

FTIR (neat) ν_{\max} : 3423, 2944, 2889, 1722, 1667, 1624, 1254 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{10}\text{H}_{15}\text{O}_2$ $[\text{M}+\text{H}]^+$: 167.1067, found: 167.1067

Wittig reaction. Synthesis of (Z)-3-(8-azido-oct-4-en-1-yl)cyclohex-2-enone (53).

To a solution of phosphonium salt **4** (793 mg, 1.8 mmol) in dry THF (25 mL) was added KHMDS (3.6 mL, 1.8 mmol, 0.5 M solution in toluene) at -78°C . After the reaction mixture was stirred for 30 min at -78°C , a solution of aldehyde **52** (200 mg, 1.20 mmol) in dry THF (15 mL) was added dropwise over 20 minutes. After 50 minutes, the reaction mixture was warmed to room temperature over 1 hour. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc (2 X 40 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (gradient from hexanes to 4:1 hexanes/EtOAc) provided compound **53** (208 mg, 70%) as a colorless oil.



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.87 (s, 1H, H-2), 5.38 (m, 2H, H-4' and H-5'), 3.27 (t, 2H, $J_{8',7'} = 6.7$ Hz, 2H-8'), 2.35 (t, 2H, $J_{6,5} = 6.6$ Hz, 2H-6), 2.28 (t, 2H, $J_{4,5} = 5.9$ Hz, 2H-4), 2.22 (t, 2H, $J_{1',2'} = 7.7$ Hz, 2H-1'), 2.15-2.03 (m, 4H, 2H-6' and 2H-3'), 1.98 (m, 2H, 2H-5), 1.69-1.53 (m, 4H, 2H-7' and 2H-2').

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 200.0 (C=O), 166.3 (C-3), 130.3 (C-4'), 129.0 (C-5'), 125.9 (C-2), 50.9 (C-8'), 37.7 (C-1'), 37.5 (C-6), 29.8 (C-4), 28.8 (C-7'), 27.0 (C-2'), 26.8 (C-3'), 24.4 (C-6'), 22.9 (C-5).

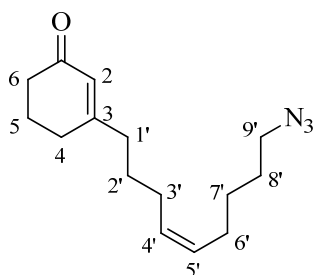
FTIR (neat) ν_{\max} : 3332, 2936, 2867, 2097, 1670, 1625, 1253 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{14}\text{H}_{22}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 248.1759, found: 248.1759

Wittig reaction. Synthesis of (Z)-3-(9-azidonon-4-en-1-yl)cyclohex-2-enone (54).

Phosphonium salt **6** (817 mg, 1.8 mmol) was dissolved in dry CH_2Cl_2 (3 mL). THF (27 mL) was added and the solution was cooled to -78°C . Then KHMDS (3.6 mL, 1.8 mmol, 0.5 M solution in toluene) was added. After the reaction mixture was stirred for 30 minutes at -78°C , a solution of aldehyde **52** (200 mg, 1.20 mmol) in dry THF (15 mL) was added dropwise over 20 minutes. After 50 minutes, the reaction mixture was warmed to room temperature over 1 hour. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc (2 X 60 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and

concentrated in vacuo. Purification of the residue by column chromatography on silica gel (gradient from hexanes to 4:1 hexanes/EtOAc) provided compound **54** (251 mg, 80%) as a colorless oil.



¹H-NMR (300 MHz, CDCl₃): δ 5.87 (s, 1H, H-2), 5.37 (m, 2H, H-4' and H-5'), 3.26 (t, 2H, $J_{9',8'} = 6.8$ Hz, 2H-9'), 2.35 (t, 2H, $J_{6,5} = 6.5$ Hz, 2H-6), 2.28 (t, 2H, $J_{4,5} = 5.6$ Hz, 2H-4), 2.21 (t, 2H, $J_{1',2'} = 7.7$ Hz, 2H-1'), 2.10-1.94 (m, 6H, 2H-5, 2H-3' and 2H-6'), 1.65-1.52 (m, 4H, 2H-8' and 2H-2'), 1.43 (m, 2H, 2H-7').

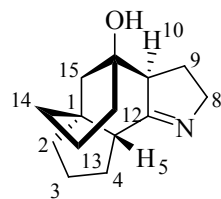
¹³C-NMR (75 MHz, CDCl₃): δ 200.0 (C=O), 166.4 (C-3), 130.1 (C-4'), 129.5 (C-5'), 125.9 (C-2), 51.5 (C-9'), 37.7 (C-1'), 37.5 (C-6), 29.8 (C-4), 28.6 (C-8'), 27.0 (C-2'), 26.8 (3C, C-3', C-6' and C-7'), 22.9 (C-5).

FTIR (neat) ν_{\max} : 3329, 2936, 2096, 1671, 1625, 1252 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₅H₂₄N₃O [M+H]⁺: 262.1914, found: 262.1917

Cyclization of **53**. Synthesis of *rac*-(1*S*,5*R*,10*S*,11*S*)-7-azatetracyclo[9.3.1.0^{1,5}.0^{6,10}]pentadec-6-en-11-ol (**55**).

To a solution of compound **53** (100 mg, 0.40 mmol) in DMF/EtOH (10 mL, 4:1) was added DBU (0.18 mL, 1.20 mmol) and the resulting mixture was heated in a microwave reactor at 120°C for 3 hours. The reaction mixture was cooled to room temperature and the solvent evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel (gradient from EtOAc to 2% MeOH in EtOAc) provided imino alcohol **55** (70 mg, 80%) as a viscous oil.



¹H-NMR (400 MHz, CDCl₃): δ 3.95 (ddt, 1H, $J_{8\alpha,8\beta} = 14.9$, $J = 9.4$, $J = 1.7$ Hz, H-8 α), 3.59 (m, 1H, H-8 β), 2.91 (t, 1H, $J = 9.9$ Hz, H-10), 2.57 (t, 1H, $J = 9.9$ Hz, H-5), 2.14-1.92 (m, 3H, H-4 α , H-9 α and H-13 α), 1.85 (m, 1H, H-15 α), 1.81-1.65 (m, 4H, 2H-3, H-4 β and H-9 β), 1.62-1.45 (m, 4H, H-12 α , H-14 α , 2H-2), 1.44-1.23 (m, 4H, H-12 β , H-13 β , H-14 β and H-15 β).

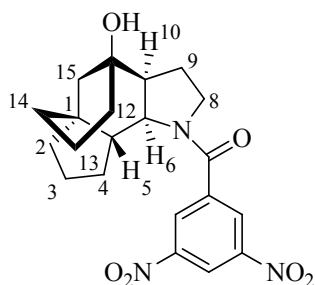
¹³C-NMR (100 MHz, CDCl₃): δ 183.5 (C=N), 73.2 (C-11), 58.6 (C-8), 55.6 (C-10), 49.4 (C-5), 47.7 (C-1), 45.9 (C-15), 39.6 (C-2), 37.3 (C-14), 34.9 (C-13), 30.0 (C-4), 23.3 (C-9), 22.2 (C-3), 21.4 (C-12).

FTIR (neat) ν_{\max} : 3339, 2934, 2870, 1640, 1451, 1047 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₄H₂₂NO [M+H]⁺: 220.1696, found: 220.1693

Synthesis of *rac*-(3,5-dinitrophenyl)[(1*S*,5*R*,6*S*,10*S*,11*S*)-11-hydroxy-7-azatetracyclo[9.3.1.0^{1,5}.0^{6,10}]pentadecan-7-yl]methanone (56).

Sodium borohydride (17 mg, 0.46 mmol) was added to a solution of compound **55** (50 mg, 0.23 mmol) in absolute ethanol (5 mL) at 0°C. After 45 minutes the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 X 30 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated in vacuo. The crude material was dissolved in CH₂Cl₂ (10 mL) and cooled to 0°C. Et₃N (64 µL, 0.46 mmol) and 3,5-dinitrobenzoyl chloride (80 mg, 0.35 mmol) were sequentially added. After stirring at room temperature for 8 hours the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from 8:2 to 3:7 hexanes/EtOAc) to afford compound **56** (54 mg, 57%) as a white solid. The relative stereochemistry of **56** was confirmed by X-ray crystallographic analysis.⁹



¹H-NMR (400 MHz, CDCl₃): δ 9.10 (t, 1H, *J* = 2.1 Hz, Ar-H), 8.71 (d, 2H, *J* = 1.9 Hz, Ar-H), 4.40 (dd, 1H, *J*_{6,5} = 9.2, *J*_{6,10} = 4.3 Hz, H-6), 3.66 (m, 1H, H-8α), 3.34 (m, 1H, H-8β), 2.51 (m, 1H, H-10), 2.22 (m, 2H, H-9α and H-13α), 2.00 (m, 1H, H-9β), 1.87 (m, 4H, 2H-12, H-5 and H-4α), 1.74-1.50 (m, 6H, 2H-3, H-15α, H-13β and 2H-2), 1.43-1.22 (m, 4H, 2H-14, H-4β and H-15β).

¹³C-NMR (100 MHz, CDCl₃): δ 166.2 (C=O), 148.5 (2C, Ar-C), 140.7 (Ar-C), 127.9 (2C, Ar-C), 120.2 (Ar-C), 72.3 (C-11), 62.7 (C-6), 50.7 (C-8), 47.8 (2C, C-10 and C-15), 46.8 (C-5), 44.5 (C-1), 42.0 (C-2), 38.5 (C-14), 35.4 (C-4), 34.6 (C-13), 25.9 (C-9), 22.7 (C-3), 21.6 (C-12).

FTIR (KBr) ν_{max}: 3459, 2931, 1626, 1545, 1341 cm⁻¹.

HRMS-ESI (m/z): calcd for C₂₁H₂₆N₃O₆ [M+H]⁺: 416.1816, found: 416.1825

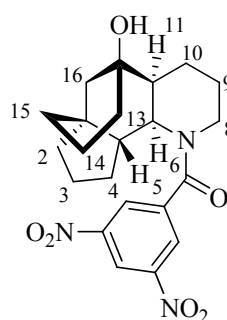
Mp: 215-218°C

Synthesis of *rac*-(3,5-dinitrophenyl)[(1*S*,5*R*,6*S*,11*S*,12*S*)-12-hydroxy-7-azatetracyclo[10.3.1.0^{1,5}.0^{6,11}]hexadecan-7-yl]methanone (58).

A solution of compound **54** (100 mg, 0.38 mmol) in DMF (10 mL) was heated in a microwave reactor at 120°C for 3 hours. The mixture was cooled to room temperature and the

⁹ Los datos de difracción de rayos X del compuesto **56** se encuentran en el anexo II.

solvent evaporated under reduced pressure. The resulting reaction crude was then passed through a plug of neutral alumina (2% methanol in dichloromethane) to remove the nonpolar impurities and afforded imino alcohol as a viscous oil. The crude material was dissolved in absolute ethanol (5 mL), cooled to 0°C and sodium borohydride (29 mg, 0.76 mmol) was added. After 50 minutes the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 X 30 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated in vacuo. The crude oil was dissolved in CH₂Cl₂ (5 mL), cooled to 0°C and Et₃N (0.11 mL, 0.76 mmol) and 3-5-dinitrobenzoyl chloride (131 mg, 0.57 mmol) were added sequentially. After stirring at room temperature for 8 hours the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from 7:3 to 3:7 hexanes/EtOAc) to afford compound **58** (65 mg, 40% from **54**, 3 steps) as a white solid.



¹H-NMR [400 MHz, CDCl₃, mixture of two conformers (4 : 1), major conformer]: δ 9.07 (t, 1H, *J* = 2.09 Hz, Ar-H), 8.51 (d, 2H, *J* = 2.09 Hz, Ar-H), 5.04 (dd, 1H, *J*_{6,5} = 13.0, *J*_{6,11} = 7.2 Hz, H-6), 3.36 (m, 1H, H-8α), 3.10 (td, 1H, *J* = 13.0, *J* = 2.0 Hz, H-8β), 2.13 (m, 1H, H-11), 2.05 (m, 1H, H-16α), 1.95 (m, 3H, H-5, H-14α and H-13α), 1.81-1.52 (m, 10H, H-9α, H-13β, 2H-3, 2H-2, 2H-4 and 2H-10), 1.51-1.30 (m, 2H, H-15α and H-9β), 1.28-1.14 (m, 3H, H-14β, H-15β and H-16β).

¹³C-NMR [100 MHz, CDCl₃, mixture of two conformers (2 : 1), major conformer]: δ 166.4 (C=O), 148.7 (2C, Ar-C), 140.6 (Ar-C), 127.1 (2C, Ar-C), 119.4 (Ar-C), 73.7 (C-12), 51.5 (C-6), 45.8 (C-16), 44.8 (C-11), 44.4 (C-1), 44.1 (C-8), 42.4 (C-2), 39.5 (C-5), 37.9 (C-15), 36.3 (C-14), 30.9 (C-4), 26.6 (C-9), 24.4 (C-10), 21.7 (C-3), 21.1 (C-13).

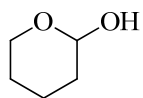
FTIR (KBr) ν_{max}: 3436, 2935, 2863, 1630, 1545, 1466, 1345, 730 cm⁻¹.

HRMS-ESI (m/z): calcd for C₂₂H₂₈N₃O₆ [M+H]⁺: 430.1973, found: 430.1978

Mp: 98-100°C

2.3.3.- Synthesis of bicyclic imines.

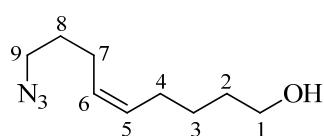
2.3.3.1.- Synthesis of no fused bicyclic pirrolines.



Synthesis of tetrahydro-2H-pyran-2-ol (59): 2,3-dihydropyran (5.0 g, 59.5 mmol) was added over a 2.0 M HCl aqueous solution (25 mL) at 0°C, stirred for 15 min, then stirred at room temperature for 1 hour. The reaction was quenched with saturated NaHCO₃ solution and the resultant mixture was extracted with CH₂Cl₂. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated in vacuo to afford hemiacetal **59** (5.29 g, 87%) as a colorless oil. The product was directly used for the Wittig reaction without further purification.

Wittig reaction. Synthesis of (Z)-9-azidonon-5-en-1-ol (60).

Phosphonium salt **4** (6.47 g, 14.7 mmol) was dissolved in dry CH₂Cl₂ (5 mL) at room temperature. THF was added (45 mL) and the mixture was cooled to -78°C. Then KHMDS (29.4 mL, 14.7 mmol, 0.5 M solution in toluene) was added. After the reaction mixture was stirred for 30 minutes at -78°C, a solution of aldehyde **59** (1 g, 9.80 mmol) in dry THF (30 mL) was added dropwise over 25 minutes. After 1 hour, the reaction mixture was warmed to room temperature over 1 hour and was stirred for an additional 3 hours. The reaction was quenched with saturated NH₄Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) provided compound **60** as a colorless oil (1.26 g, 70%).



¹H-NMR (300 MHz, CDCl₃): δ 5.42 (m, 1H, H-5), 5.33 (m, 1H, H-6), 3.65 (t, 2H, *J*_{1,2} = 6.5 Hz, 2H-1), 3.27 (t, 2H, *J*_{9,8} = 6.8 Hz, 2H-9), 2.16-2.02 (m, 4H, 2H-4 and 2H-7), 1.64 (m, 2H, 2H-8), 1.57 (m, 2H, 2H-2), 1.43 (m, 2H, 2H-3).

¹³C-NMR (75 MHz, CDCl₃): δ 131.1 (C-5), 128.4 (C-6), 63.0 (C-1), 51.0 (C-9), 32.5 (C-2), 28.8 (C-8), 27.0 (C-4), 25.9 (C-3), 24.4 (C-7).

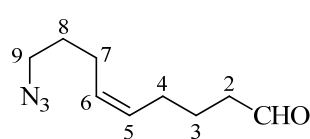
FTIR (neat) ν_{max}: 3350, 2935, 2863, 2097, 1453, 1287, 1255, 1062 cm⁻¹.

HRMS-ESI (m/z): calcd for C₉H₁₈N₃O [M+H]⁺: 184.1444, found: 184.1448

Oxidation of alcohol **60**. Synthesis of (Z)-9-azidonon-5-enal (61).

PCC (1885 mg, 8.74 mmol) was added to a solution of **60** (800 mg, 4.37 mmol) in CH₂Cl₂ (20 mL) at room temperature. The mixture was stirred for 2 hours and then it was

filtered through a plug of Celite. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) provided compound **61** as a colorless oil (673 mg, 85%).



¹H-NMR (300 MHz, CDCl₃): δ 9.75 (s, 1H, CHO), 5.37 (m, 2H, H-5 and H-6), 3.25 (t, 2H, *J*_{9,8} = 6.8 Hz, 2H-9), 2.42 (m, 2H, 2H-2), 2.08 (m, 4H, 2H-4 and 2H-7), 1.65 (m, 4H, 2H-3 and 2H-8).

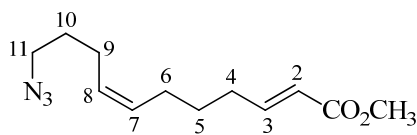
¹³C-NMR (75 MHz, CDCl₃): δ 202.5 (CHO), 129.9 (C-5), 129.3 (C-6), 50.9 (C-9), 43.3 (C-2), 28.7 (C-8), 26.5 (C-4), 24.3 (C-3), 22.0 (C-7).

FTIR (neat) ν_{max}: 3008, 2939, 2866, 2721, 2097, 1725, 1453, 1287, 1256 cm⁻¹.

HRMS-ESI (m/z): calcd for C₉H₁₆NO [M+H-N₂]⁺: 154.1231, found: 154.1228

Synthesis of (2*E*,7*Z*)-methyl 11-azidoundeca-2,7-dienoate (**62**).

To a solution of **61** (200 mg, 1.10 mmol) in CH₂Cl₂ (30 mL) was added (methoxycarbonylmethylene)triphenylphosphorane (735 mg, 2.20 mmol) at room temperature and the mixture was stirred overnight. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 95:5 hexanes/EtOAc) to provide compound **62** as a colorless oil (238 mg, 91%).



¹H-NMR (300 MHz, CDCl₃): δ 6.97 (dt, 1H, *J*_{3,2} = 15.7, *J*_{3,4} = 7.0 Hz, H-3), 5.83 (dt, 1H, *J*_{2,3} = 15.7, *J*_{2,4} = 1.4 Hz, H-2), 5.38 (m, 2H, H-7 and H-8), 3.73 (s, 3H, CO₂CH₃), 3.27 (t, 2H, *J*_{11,10} = 6.8 Hz, 2H-11), 2.22 (m, 2H, 2H-4), 2.11 (m, 4H, 2H-9 and 2H-6), 1.65 (m, 2H, 2H-10), 1.53 (m, 2H, 2H-5).

¹³C-NMR (75 MHz, CDCl₃): δ 167.2 (CO₂CH₃), 149.3 (C-3), 130.4 (C-7), 128.9 (C-8), 121.3 (C-2), 51.5 (CO₂CH₃), 51.0 (C-11), 31.8 (C-4), 28.9 (C-10), 28.1 (C-5), 26.7 (C-6), 24.5 (C-9).

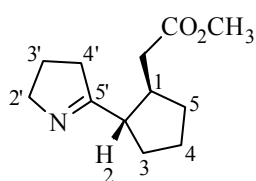
FTIR (neat) ν_{max}: 3008, 2935, 2861, 2097, 1724, 1659, 1455, 1436, 1345, 1271, 1202, 1177, 1152, 1040, 979, 719 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₂H₂₀N₃O₂ [M+H]⁺: 238.1550, found: 238.1548

Cyclization of **62**. Synthesis of *rac*-methyl 2-[(1*R*,2*S*)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)cyclopentyl]acetate (**63**).

A solution of compound **62** (70 mg, 0.29 mmol) in dry DMF (12 mL) was heated in a microwave reactor at 140°C for 2 hours. The mixture was cooled to room temperature and the

solvent evaporated under reduced pressure. The crude reaction was then purified by column chromatography (silica gel, gradient from CH₂Cl₂ to 98:2 CH₂Cl₂/MeOH) to afford compound **63** (48 mg, 78%) as a yellow oil.



¹H-NMR (400 MHz, CDCl₃): δ 3.75 (m, 2H, 2H-2'), 3.61 (s, 3H, CO₂CH₃), 2.47 (m, 4H, H-2, 2H-4', CH₂CO₂CH₃), 2.39 (m, 1H, H-1), 2.23 (dd, 1H, *J* = 14.9, *J* = 8.3 Hz, CH₂CO₂CH₃), 2.02-1.86 (m, 2H, H-5α and H-3α), 1.83 (m, 2H, 2H-3'), 1.66 (m, 3H, 2H-4 and H-3β), 1.29

(m, 1H, H-5β).

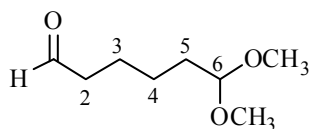
¹³C-NMR (100 MHz, CDCl₃): δ 180.1 (C=N), 173.6 (CO₂CH₃), 60.6 (C-2'), 51.5 (CO₂CH₃), 49.8 (C-2), 40.1 (C-1), 39.1 (CH₂CO₂CH₃), 34.8 (C-4'), 32.4 (C-5), 30.6 (C-3), 24.2 (C-4), 22.6 (C-3').

FTIR (neat) v_{max}: 2952, 2869, 1738, 1637, 1436, 1372, 1295, 1255, 1197, 1175, 1017 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₂H₂₀NO₂ [M+H]⁺: 210.1489, found: 210.1499

Ozonolysis of cyclohexene. Synthesis of 6,6-dimethoxyhexanal (**64**).

A solution of cyclohexene (1 g, 12.17 mmol) in CH₂Cl₂ (100 mL) and MeOH (50 mL) was ozonized at -78°C. After the solution turned blue the reaction mixture was flushed with oxygen until clear and then the cold bath was removed. *p*-Toluenesulfonic acid (197 mg, 1.14 mmol) was added and the solution was allowed to warm to room temperature for 90 minutes. Anhydrous sodium bicarbonate (348 mg, 4.14 mmol) was added and the mixture was stirred for 15 minutes. Then triphenylphosphine (7.8 g, 30.0 mmol) was added and the solution was stirred overnight. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) to provide compound **64** as a colorless oil (1248 mg, 64%).



¹H-NMR (300 MHz, CDCl₃): δ 9.67 (s, 1H, CHO), 4.26 (t, 1H, *J*_{6,5} = 5.6 Hz, H-6), 3.21 (s, 6H, OCH₃), 2.35 (t, 2H, *J*_{2,3} = 7.3, 2H-2), 1.53 (m, 4H, 2H-5 and 2H-3), 1.31 (m, 2H, 2H-4).

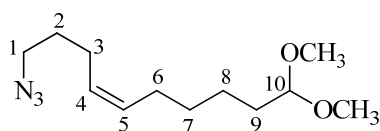
¹³C-NMR (75 MHz, CDCl₃): δ 202.4 (CHO), 104.2 (C-6), 52.7 (2C, OCH₃), 43.7 (C-2), 32.2 (C-5), 24.1 (C-4), 21.8 (C-3).

FTIR (neat) v_{max}: 2947, 2831, 2723, 1725, 1462, 1389, 1129, 1052, 961 cm⁻¹.

HRMS-ESI (m/z): calcd for C₈H₁₇O₃ [M+H]⁺: 161.1172, found: 161.1174

Wittig reaction. Synthesis of (Z)-1-azido-10,10-dimethoxydec-4-ene (65).

Phosphonium salt **4** (4.12 g, 9.36 mmol) was dissolved in dry CH_2Cl_2 (5 mL). THF (45 mL) was added and the solution was cooled to -78°C . Then KHMDS (18.7 mL, 9.36 mmol, 0.5 M solution in toluene) was added. After the reaction mixture was stirred for 30 minutes at -78°C , a solution of aldehyde **64** (1 g, 6.24 mmol) in dry THF (30 mL) was added dropwise over 20 minutes. After 50 minutes, the reaction mixture was warmed to room temperature over 2 hours. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) yielded compound **65** as a colorless oil (979 mg, 65%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.41 (m, 1H, H-5), 5.32 (m, 1H, H-4), 4.35 (t, 1H, $J_{10,9} = 5.7$ Hz, H-10), 3.31 (s, 6H, OCH_3), 3.26 (t, 2H, $J_{1,2} = 7.0$ Hz, 2H-1), 2.11 (m, 2H, 2H-3), 2.03 (m, 2H, 2H-6), 1.64 (m, 2H, 2H-2), 1.60 (m, 2H, 2H-9), 1.36 (m, 4H, 2H-7 and 2H-8).

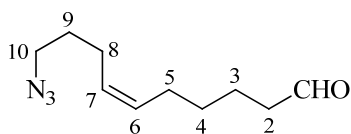
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 131.2 (C-5), 128.1 (C-4), 104.6 (C-10), 52.8 (2C, OCH_3), 51.0 (C-1), 32.5 (C-9), 29.6 (C-7), 28.9 (C-2), 27.2 (C-6), 24.4 (2C, C-3 and C-8).

FTIR (neat) ν_{max} : 2943, 2097, 1455, 1256, 1130, 1074, 1053 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{12}\text{H}_{24}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 214.1803, found: 214.1803

Deprotection of 65. Synthesis of (Z)-10-azidodec-6-enal (66).

To a solution of **65** (500 mg, 2.07 mmol) in THF/ H_2O (30 mL, 1:1) was added pyridinium *p*-toluenesulfonic acid (1.04 g, 4.14 mmol) at room temperature and the solution was warmed to 50°C for 4 hours. After being cooled to room temperature, the reaction was then diluted with water (10 mL) and with Et_2O (15 mL). The aqueous phase was extracted with Et_2O (3 X 40 mL). The combined organic layers were washed with sat. aq. NH_4Cl solution, brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) provided compound **66** as a colorless oil (364 mg, 90%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 9.76 (s, 1H, CHO), 5.37 (m, 2H, H-7 and H-6), 3.27 (t, 2H, $J_{10,9} = 6.8$ Hz, 2H-10), 2.43 (t, 2H, $J_{2,3} = 7.3$, 2H-2), 2.10 (m, 4H, 2H-8 and 2H-5), 1.64 (m, 4H, 2H-9 and 2H-3), 1.40 (m, 2H, 2H-4).

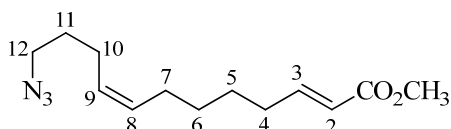
^{13}C -NMR (75 MHz, CDCl_3): δ 202.8 (CHO), 130.7 (C-6), 128.6 (C-7), 50.9 (C-10), 43.9 (C-2), 29.2 (C-4), 28.8 (C-9), 27.0 (C-5), 24.4 (C-8), 21.8 (C-3).

FTIR (neat) ν_{max} : 2935, 2861, 2721, 2097, 1725, 1453, 1287, 1255 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{10}\text{H}_{17}\text{N}_3\text{NaO}$ $[\text{M}+\text{Na}]^+$: 218.1264, found: 218.1263

Synthesis of (2E,8Z)-methyl 12-azidododeca-2,8-dienoate (67).

To a solution of **66** (200 mg, 1.02 mmol) in CH_2Cl_2 (30 mL) was added (methoxycarbonylmethylene)triphenylphosphorane (684 mg, 2.04 mmol) at room temperature and the mixture was stirred overnight. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 95:5 hexanes/EtOAc) to provide compound **67** as a colorless oil (215 mg, 84%).



^1H -NMR (300 MHz, CDCl_3): δ 6.96 (dt, 1H, $J_{3,2} = 15.6$, $J_{3,4} = 7.0$ Hz, H-3), 5.81 (dt, 1H, $J_{2,3} = 15.6$, $J_{2,4} = 1.5$ Hz, H-2), 5.36 (m, 2H, H-9 and H-8), 3.72 (s, 3H, COCH_3), 3.27 (t, 2H, $J_{12,11} = 6.8$ Hz, 2H-12), 2.20 (m, 2H, 2H-4), 2.10 (m, 2H, 2H-10), 2.04 (m, 2H, 2H-7), 1.64 (m, 2H, 2H-11), 1.47 (m, 2H, 2H-5), 1.38 (m, 2H, 2H-6).

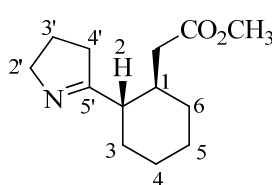
^{13}C -NMR (75 MHz, CDCl_3): δ 167.3 (CO_2CH_3), 149.6 (C-3), 130.8 (C-8), 128.4 (C-9), 121.1 (C-2), 51.5 (CO_2CH_3), 51.0 (C-12), 32.2 (C-4), 29.2 (C-6), 28.8 (C-11), 27.7 (C-5), 27.0 (C-7), 24.4 (C-10).

FTIR (neat) ν_{max} : 3007, 2933, 2859, 2097, 1725, 1657, 1436, 1271, 1200, 1176, 1041, 981, 848, 718 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{13}\text{H}_{21}\text{N}_3\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 274.1526, found: 274.1523

Cyclization of 67. Synthesis of *rac*-methyl 2-[(1R,2S)-2-(3,4-dihydro-2H-pyrrol-5-yl)cyclohexyl]acetate (68).

A solution of compound **67** (70 mg, 0.28 mmol) in DMF (10 mL) was heated in a microwave reactor at 140°C for 2 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The resulting reaction crude was then purified by column chromatography (silica gel, gradient from CH_2Cl_2 to 98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford compound **68** (51 mg, 82%) as a pale yellow oil.



¹H-NMR (400 MHz, CDCl₃): δ 3.75 (m, 2H, 2H-2'), 3.62 (s, 3H, COCH₃), 2.44 (m, 2H, 2H-4'), 2.29 (dd, 1H, $J = 14.6$, $J = 3.5$ Hz, CH₂CO₂CH₃), 2.23 (m, 1H, H-2), 2.02 (dd, 1H, $J = 14.6$, $J = 8.8$ Hz, CH₂CO₂CH₃), 1.98 (m, 1H, H-1), 1.87-1.70 (m, 6H, 2H-4, H-6 α , 2H-3' and H-3 α), 1.35 (m, 1H, H-3 β), 1.26 (m, 2H, 2H-5), 1.04 (m, 1H, H-6 β).

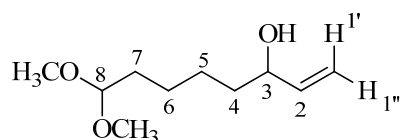
¹³C-NMR (100 MHz, CDCl₃): δ 181.0 (C=N), 173.6 (CO₂CH₃), 60.5 (C-2'), 51.5 (CO₂CH₃), 48.1 (C-2), 39.7 (CH₂CO₂CH₃), 36.7 (C-1), 34.3 (C-4'), 32.4 (C-6), 30.8 (C-3), 25.9 (C-4), 25.7 (C-5), 22.4 (C-3').

FTIR (neat) ν_{\max} : 2928, 2857, 1736, 1637, 1447, 1437, 1289, 1231, 1163, 1102, 1018, 1002, 974 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₃H₂₂NO₂ [M+H]⁺: 224.1645, found: 224.1650

Synthesis of 8,8-dimethoxyoct-1-en-3-ol (**69**).

To a stirred solution of compound **64** (1.0 g, 6.25 mmol) in THF (30 mL) at -78°C, vinylmagnesium bromide (1M in THF, 12.5 mL, 12.5 mmol) was added dropwise. After 3 hours, the reaction was quenched with saturated NH₄Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) provided compound **69** as a colorless oil (975 mg, 83%).



¹H-NMR (400 MHz, CDCl₃): δ 5.86 (ddd, 1H, $J_{2,1'} = 17.2$, $J_{2,1''} = 10.4$, $J_{2,3} = 6.2$ Hz, H-2), 5.22 (dt, 1H, $J_{1',2} = 17.2$, $J_{1',1''} = 1.4$ Hz, H-1'), 5.10 (dt, 1H, $J_{1'',2} = 10.4$, $J_{1'',1'} = 1.4$ Hz, H-1''), 4.36 (t, 1H, $J_{8,7} = 5.7$ Hz, H-8), 4.01 (m, 1H, H-3), 3.31 (s, 6H, OCH₃), 1.68-1.47 (m, 4H, 2H-4 and 2H-7), 1.43-1.30 (m, 4H, 2H-5 and 2H-6).

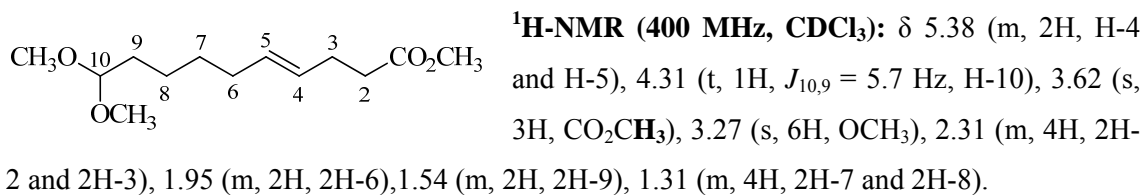
¹³C-NMR (100 MHz, CDCl₃): δ 141.5 (C-2), 114.6 (C-1), 104.9 (C-8), 73.2 (C-3), 52.9 (2C, OCH₃), 37.2 (C-4), 32.7 (C-7), 25.3 (C-5), 24.7 (C-6).

FTIR (neat) ν_{\max} : 3391, 2943, 1643, 1433, 1126, 1052 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₀H₂₀NaO₃ [M+Na]⁺: 211.1305, found: 211.1301

Claisen-Johnson rearrangement. Synthesis of (*E*)-methyl 10,10-dimethoxydec-4-enoate (**70**).

A solution of compound **69** (800 mg, 4.25 mmol) in trimethyl ortoacetate (15 mL) was heated to 100°C, and then propionic acid (three drops) was added. The mixture was stirred for 1.5 hours at 140°C. The solvent was evaporated, and the residual product was purified by flash chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) to afford compound **70** as a colorless oil (943 mg, 91%).



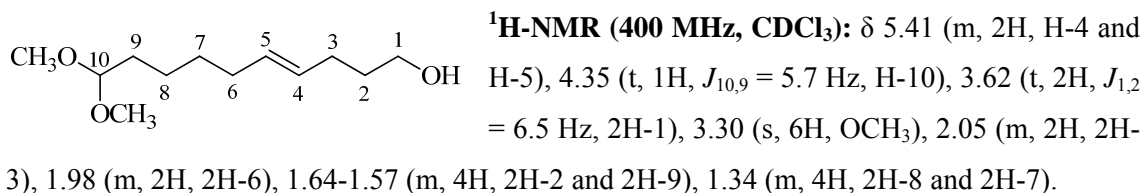
¹³C-NMR (100 MHz, CDCl₃): δ 173.6 (C=O), 131.6 (C-5), 128.4 (C-4), 104.8 (C-10), 52.7 (2C, OCH₃), 51.4 (CO₂CH₃), 34.3 (C-9), 32.6 (C-2), 32.5 (C-6), 29.4 (C-7), 28.0 (C-3), 24.2 (C-8).

FTIR (neat) v_{max}: 3368, 2946, 1741, 1437, 1128 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₃H₂₄NaO₄ [M+Na]⁺: 267.1567, found: 267.1563

Reduction of methyl ester **70**. Synthesis of (*E*)-10,10-dimethoxydec-4-en-1-ol (**71**).

To a stirred solution of compound **70** (800 mg, 3.27 mmol) in THF (20 mL) at -10°C, LiBH₄ (214 mg, 9.8 mmol) was added. After 5 minutes, MeOH (2 mL) was slowly added dropwise and the mixture was allowed to warm to room temperature. After 4 hours the reaction was quenched with saturated NH₄Cl solution and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 1:1 hexanes/EtOAc) afforded compound **71** as a colorless oil (501 mg, 71%).



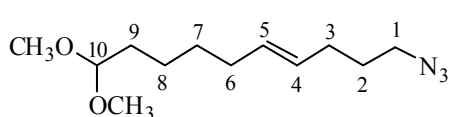
¹³C-NMR (100 MHz, CDCl₃): δ 131.0 (C-5), 129.9 (C-4), 104.9 (C-10), 62.6 (C-1), 52.8 (2C, OCH₃), 32.7 (C-9), 32.6 (C-6), 32.5 (C-2), 29.5 (C-7), 29.0 (C-3), 24.2 (C-8).

FTIR (neat) v_{max}: 3369, 2935, 1632, 1446, 1128, 1053 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₂H₂₄NaO₃ [M+Na]⁺: 239.1618, found: 239.1617

Synthesis of (*E*)-1-azido-10,10-dimethoxydec-4-ene (72).

Et₃N (0.64 mL, 4.62 mmol) was added to a solution of alcohol **71** (400 mg, 1.85 mmol) in dry CH₂Cl₂ (20 mL) at 0°C under argon. After 5 minutes of stirring, a solution of methanesulfonyl chloride (0.184 mL, 2.40 mmol) in dry CH₂Cl₂ (5 mL) was added. The reaction mixture was allowed to warm up to room temperature for 1 hour and quenched by addition of saturated solution of NaHCO₃. The organic phase was washed with water, HCl (5%) and brine, dried (MgSO₄), and the solvents evaporated to afford the corresponding mesylate as a colorless oil which was used immediately without further purification. The above obtained compound was dissolved in dry DMF (25 mL) and NaN₃ (1.20 g, 18.5 mmol) was added. The mixture was stirred at 50°C for 7 hours and then the solvent was concentrated in vacuo, EtOAc was added to the residue and washed with H₂O twice. The organic phase was dried (MgSO₄), and the solvent was evaporated. Purification of the residual product by flash chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) afforded azide **72** as a colorless oil (343 mg, 77%).



¹H-NMR (400 MHz, CDCl₃): δ 5.38 (m, 2H, H-4 and H-5), 4.34 (t, 1H, *J*_{10,9} = 5.7 Hz, H-10), 3.29 (s, 6H, OCH₃), 3.35 (t, 2H, *J*_{1,2} = 6.9 Hz, 2H-1), 2.06 (m, 2H, 2H-3), 1.98 (m, 2H, 2H-6), 1.63 (m, 2H, 2H-2), 1.58 (m, 2H, 2H-9), 1.34 (m, 4H, 2H-7 and 2H-8).

¹³C-NMR (100 MHz, CDCl₃): δ 131.8 (C-5), 128.8 (C-4), 104.8 (C-10), 52.8 (2C, OCH₃), 51.0 (C-1), 32.7 (2C, C-6 and C-9), 29.7 (C-2), 29.5 (C-7), 28.9 (C-3), 24.2 (C-8).

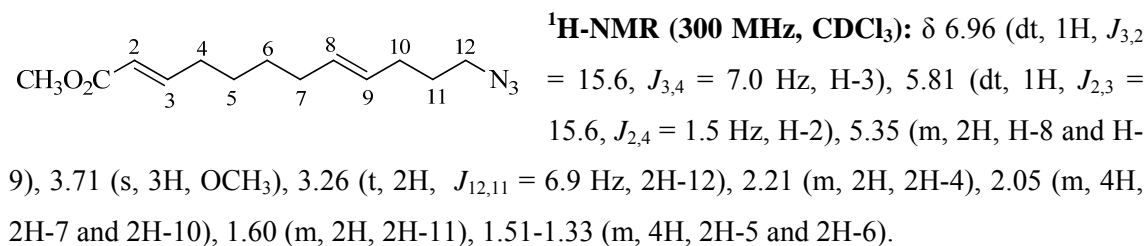
FTIR (neat) ν_{max}: 2941, 2098, 1453, 1232, 1052 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₂H₂₃N₃NaO₂[M+Na]⁺: 264.1682, found: 264.1692

Synthesis of (2*E*,8*E*)-methyl 12-azidododeca-2,8-dienoate (73).

To a solution of **72** (300 mg, 1.24 mmol) in THF/H₂O (20 mL, 1:1) was added pyridinium *p*-toluenesulfonic acid (623 mg, 2.48 mmol) at room temperature and the solution was warmed to 50°C for 3 hours. After being cooled to room temperature, the reaction was then diluted with water (10 mL) and with Et₂O (15 mL). The aqueous phase was extracted with Et₂O (3 X 20 mL). The combined organic layers were washed with sat. aq. NH₄Cl solution, brine, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was dissolved in CH₂Cl₂ (50 mL) and (methoxycarbonylmethylene)triphenylphosphorane (1.242 g, 3.72 mmol) was added at room temperature. After stirring overnight, the solvent was removed and the crude product was

purified by column chromatography (silica gel, gradient from hexane to 8:2 hexanes/EtOAc) to provide compound **73** as a colorless oil (257 mg, 83%, 2 steps).



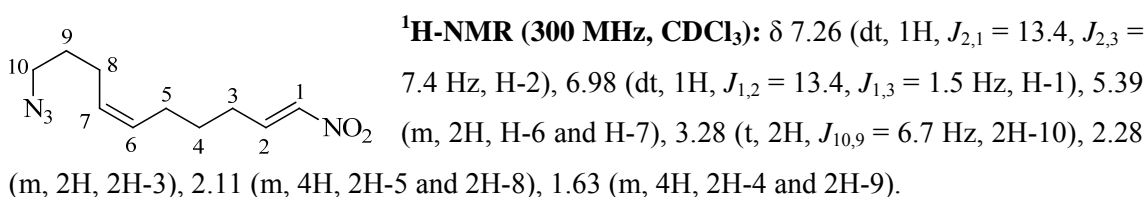
¹³C-NMR (75 MHz, CDCl₃): δ 167.3 (C=O), 149.6 (C-3), 131.4 (C-8), 129.0 (C-9), 121.2 (C-2), 51.3 (CO₂CH₃), 51.0 (C-12), 32.3 (C-7), 32.1 (C-4), 29.7 (C-11), 29.0 (C-10), 28.8 (C-6), 27.6 (C-5).

FTIR (neat) ν_{\max} : 2933, 2856, 2095, 1725, 1655, 1434, 1271 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₃H₂₁N₃NaO₂ [M+Na]⁺: 274.1526, found: 274.1528

Synthesis of (1E,6Z)-10-azido-1-nitrodeca-1,6-diene (**74**).

A mixture of aldehyde **61** (250 mg, 1.38 mmol) and nitromethane (0.07 mL, 1.38 mmol) was dissolved in methanol (5 mL) at 0°C. A solution of NaOH in H₂O (66 mg, 1.66 mmol in 1 mL) was added dropwise and the mixture was stirred for 2 hours. The reaction was quenched with saturated NH₄Cl solution and concentrated under reduced pressure to eliminate the methanol. The residue was extracted with CH₂Cl₂ (3 X 30 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was then dissolved in CH₂Cl₂ (10 mL) at 0°C and methanesulfonyl chloride (0.12 mL, 1.51 mmol) was added. In 15 minutes Et₃N (0.40 mL, 2.76 mmol) was added. The reaction mixture was stirred for 30 minutes at 0°C and then 2 hours at room temperature. After quenching with H₂O the contents were extracted with CH₂Cl₂ (3 X 30 mL). The combined organic layers were washed successively with saturated NaHCO₃ solution and brine, dried over MgSO₄, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) to afford compound **74** as a colorless oil (253 mg, 82%, 2 steps).



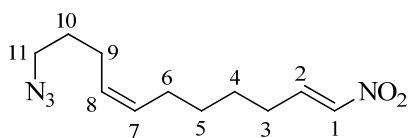
¹³C-NMR (75 MHz, CDCl₃): δ 142.5 (C-2), 139.9 (C-1), 129.7 (C-6), 129.5 (C-7), 50.9 (C-10), 28.7 (C-9), 28.1 (C-3), 27.8 (C-4), 26.7 (C-5), 24.4 (C-8).

FTIR (neat) ν_{max} : 3008, 2937, 2864, 2098, 1649, 1560, 1525, 1455, 1352, 1255, 962 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{10}\text{H}_{16}\text{N}_4\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 247.1165, found: 247.1169

Synthesis of (1*E*,7*Z*)-11-azido-1-nitroundeca-1,7-diene (75)

A mixture of aldehyde **66** (300 mg, 1.54 mmol) and nitromethane (0.08 mL, 1.54 mmol) was dissolved in methanol (5 mL) at 0°C. A solution of NaOH in H_2O (74 mg, 1.85 mmol in 1 mL) was added dropwise and the mixture was stirred for 2 hours. The reaction was quenched with saturated NH_4Cl solution and concentrated under reduced pressure to eliminate the methanol. The residue was extracted with CH_2Cl_2 (3 X 30 mL). The combined organic phases were dried over MgSO_4 , filtered, and concentrated in vacuo. The crude product was then dissolved in CH_2Cl_2 (10 mL) at 0°C and methanesulfonyl chloride (0.13 mL, 1.69 mmol) was added. In 15 min Et_3N (0.43 mL, 3.08 mmol) was added. The reaction mixture was stirred for 30 minutes at 0°C and then 2 hours at room temperature. After quenching with H_2O the contents were extracted with CH_2Cl_2 (3 X 30 mL). The combined organic layers were washed successively with saturated NaHCO_3 solution and brine, dried over MgSO_4 , filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (silica gel, gradient from hexanes to 9:1 hexanes/ EtOAc) to afford compound **75** as a colorless oil (282 mg, 77%, 2 steps).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.28 (dt, 1H, $J_{2,1} = 13.4$, $J_{2,3} = 7.4$ Hz, H-2), 6.99 (dt, 1H, $J_{1,2} = 13.4$, $J_{1,3} = 1.5$ Hz, H-1), 5.39 (m, 2H, H-7 and H-8), 3.29 (t, 2H, $J_{11,10} = 6.7$ Hz, 2H-11), 2.29 (m, 2H, 2H-3), 2.12 (m, 4H, 2H-6 and 2H-9), 1.66 (m, 2H, 2H-10), 1.54 (m, 2H, 2H-4), 1.43 (m, 2H, 2H-5).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 142.6 (C-2), 139.8 (C-1), 130.5 (C-7), 128.8 (C-8), 50.9 (C-11), 29.2 (C-5), 28.8 (C-10), 28.5 (C-3), 27.4 (C-4), 26.9 (C-6), 24.4 (C-9).

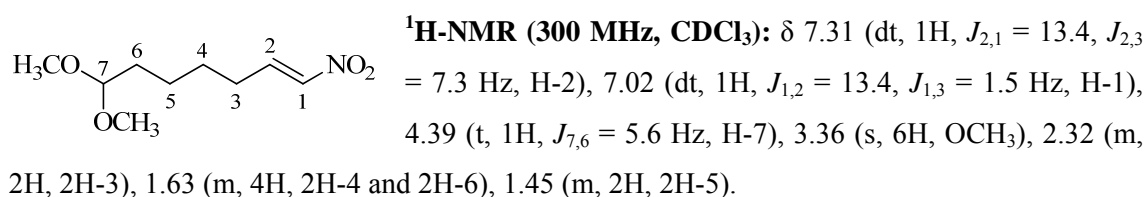
FTIR (neat) ν_{max} : 2935, 2861, 2097, 1559, 1525, 1350 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{11}\text{H}_{18}\text{N}_4\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 261.1322, found: 261.1326

Synthesis of (E)-7,7-dimethoxy-1-nitrohept-1-ene (76)

A mixture of aldehyde **64** (500 mg, 3.12 mmol) and nitromethane (0.17 mL, 3.12 mmol) was dissolved in methanol (10 mL) at 0°C. A solution of NaOH in H_2O (150 mg, 3.74 mmol in 2 mL) was added dropwise and the mixture was stirred for 2 hours. The reaction was quenched with saturated NH_4Cl solution and concentrated under reduced pressure to eliminate the

methanol. The residue was extracted with CH_2Cl_2 (3 X 30 mL). The combined organic phases were dried over MgSO_4 , filtered, and concentrated in vacuo. The crude product was then dissolved in CH_2Cl_2 (30 mL) at 0°C and methanesulfonyl chloride (0.27 mL, 3.43 mmol) was added. In 15 min Et_3N (0.87 mL, 6.24 mmol) was added. The reaction mixture was stirred for 30 minutes at 0°C and then 2 hours at room temperature. After quenching with H_2O the contents were extracted with CH_2Cl_2 (3 X 30 mL). The combined organic layers were washed successively with saturated NaHCO_3 solution and brine, dried over MgSO_4 , filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (silica gel, gradient from hexanes to 8:2 hexanes/ EtOAc) to afford compound **76** as a colorless oil (425 mg, 67%, 2 steps).



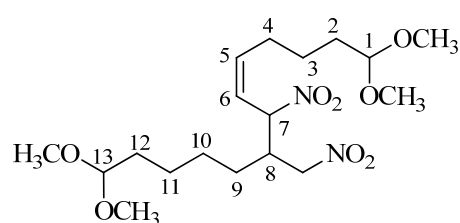
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 142.6 (C-2), 139.8 (C-1), 104.4 (C-7), 53.0 (2C, OCH_3), 32.3 (C-6), 28.5 (C-3), 27.7 (C-4), 24.2 (C-5).

FTIR (neat) ν_{max} : 2947, 2831, 1650, 1526, 1354, 1129, 1074, 1054, 955 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_9\text{H}_{16}\text{NO}_3$ $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$: 186.1125, found: 186.1121

Synthesis of (E)-1,1,13,13-tetramethoxy-7-nitro-8-(nitromethyl)tridec-5-ene (**77**).

A solution of **76** (50 mg, 0.25 mmol) in dry DMF (10 mL) was heated in a sealed tube at 80°C for 6 hours. Then the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/ EtOAc) to obtain compound **77** as an inseparable 1:1 mixture of diastereomers (30 mg, 30%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.94 (dt, 1H, $J_{5,6} = 10.1$, $J_{5,4} = 7.4$ Hz, H-5), 5.59 (m, 1H, H-6), 5.47 (ddd, 1H, $J = 10.1$, $J = 7.6$, $J = 2.3$ Hz, H-7), 4.59-4.39 (m, 2H, CH_2NO_2), 4.34 (m, 2H, H-13 and H-1), 3.21 (s, 12H, OCH_3), 2.83 (m, 1H, H-8), 2.33-2.12 (m, 2H, 2H-4), 1.59 (m, 4H, 2H-2 and 2H-12), 1.53-1.29 (m, 8H, 2H-3, 2H-9, 2H-10 and 2H-11).

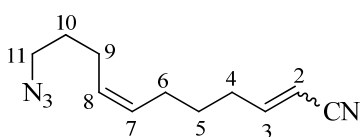
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 141.7 (C-5), 140.7 (C-5), 121.4 (C-6), 120.9 (C-6), 104.4 (2C, C-1 and C-13), 85.6 (C-7), 84.5 (C-7), 75.1 (CH_2NO_2), 74.5 (CH_2NO_2), 53.0 (4C, OCH_3), 41.0 (C-8), 40.9 (C-8), 32.2 (C-12), 32.0 (C-2), 28.1 (C-9), 27.8 (C-4), 27.7 (C-4), 26.4 (C-10), 26.3 (C-10), 24.4 (C-11), 24.1 (C-3).

FTIR (neat) ν_{\max} : 3445, 2946, 2867, 1555, 1381, 1365, 1128, 1071, 952 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{18}\text{H}_{38}\text{N}_3\text{O}_8$ $[\text{M}+\text{NH}_4]^+$: 424.2653, found: 424.2662

Synthesis of (7Z)-11-azidoundeca-2,7-dienenitrile (78).

A suspension of NaH (83 mg of 60% in mineral oil, 2.07 mmol) in dry THF (20 mL) was cooled to 0°C. Diethyl(cyanomethyl)phosphonate (0.33 mL, 2.07 mmol) was added dropwise and the reaction mixture was warmed to room temperature over 1 hour. Then a solution of **61** (250 mg, 1.38 mmol) in dry THF (10 mL) was added dropwise at room temperature and the mixture was stirred for 4 hours. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) yielded compound **78** as a colorless oil (220 mg, 78%).



^1H -NMR (300 MHz, CDCl_3 , 45:55 mixture of *E/Z* isomers):

δ 6.72 (dt, 0.45H, $J_{3,2} = 16.3$, $J_{3,4} = 6.9$ Hz, H-3, *E* isomer), 6.48 (dt, 0.55H, $J_{3,2} = 10.9$, $J_{3,4} = 7.7$ Hz, H-3, *Z* isomer), 5.36 (m, 3H, H-2, H-7 and H-8), 3.28 (t, 2H, $J_{11,10} = 6.8$ Hz, 2H-11), 2.44 (m, 0.9H, H-4, *E* isomer), 2.23 (m, 1.1H, H-4, *Z* isomer), 2.09 (m, 4H, 2H-9 and 2H-6), 1.66 (m, 2H, 2H-10), 1.53 (m, 2H, 2H-5).

^{13}C -NMR (75 MHz, CDCl_3 , 45:55 mixture of *E/Z* isomers): δ 155.8 (C-3, *E* isomer), 154.9 (C-3, *Z* isomer), 130.0 (C-7), 129.2 (C-8), 117.6 (CN, *Z* isomer), 116.1 (CN, *E* isomer), 100.0 (C-2), 50.9 (C-11), 32.9 (C-4, *E* isomer), 31.6 (C-4, *Z* isomer), 28.8 (C-10), 28.3 (C-5, *E* isomer), 27.7 (C-5, *Z* isomer), 26.7 (C-6), 24.4 (C-9).

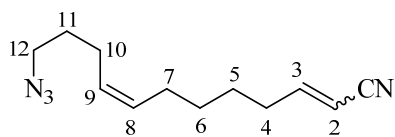
FTIR (neat) ν_{\max} : 3009, 2937, 2863, 2222, 2097, 1633, 1455, 1287, 1256, 968, 739 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{11}\text{H}_{16}\text{N}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 227.1267, found: 227.1266

Synthesis of (8Z)-12-azidododeca-2,8-dienenitrile (79).

A suspension of NaH (61 mg of 60% in mineral oil, 1.53 mmol) in dry THF (20 mL) was cooled to 0°C. Diethyl (cyanomethyl)phosphonate (0.24 mL, 1.53 mmol) was added dropwise and the reaction mixture was warmed to room temperature over 1 hour. Then a solution of **66** (200 mg, 1.02 mmol) in dry THF (10 mL) was added dropwise at room temperature and the mixture was stirred for 4 hours. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over

MgSO₄, filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 95:5 hexanes/EtOAc) yielded compound **79** as a colorless oil (205 mg, 92%).



¹H-NMR (300 MHz, CDCl₃, mixture 4:6 of *E/Z* isomers):

δ 6.71 (dt, 0.4H, *J*_{3,2} = 16.3, *J*_{3,4} = 7.1 Hz, H-3, *E* isomer), 6.47 (dt, 0.6H, *J*_{3,2} = 10.9, *J*_{3,4} = 7.6 Hz, H-3, *Z* isomer), 5.34 (m, 3H, H-9, H-8 and H-2), 3.28 (t, 2H, *J*_{12,11} = 6.8 Hz, 2H-12), 2.43 (m, 1.20H, H-4, *Z* isomer), 2.23 (m, 0.8H, H-4, *E* isomer), 2.10 (m, 4H, 2H-10 and 2H-7), 1.64 (m, 2H, 2H-11), 1.42 (m, 4H, 2H-6 and 2H-5).

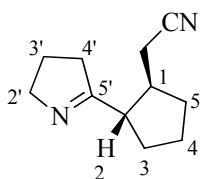
¹³C-NMR (75 MHz, CDCl₃, mixture 4:6 of *E/Z* isomers): δ 156.0 (C-3, *E* isomer), 155.1 (C-3, *Z* isomer), 130.7 (C-8), 128.6 (C-9), 117.7 (CN, *E* isomer), 116.2 (CN, *Z* isomer), 100.0 (C-2, *E* isomer), 99.8 (C-2, *Z* isomer), 51.0 (C-12), 33.4 (C-4, *E* isomer), 31.9 (C-4, *Z* isomer), 29.1 (C-6), 28.9 (C-11), 27.9 (C-5), 27.0 (C-7), 24.4 (C-10).

FTIR (neat) v_{max}: 3008, 2935, 2860, 2221, 2097, 1633, 1622, 1453, 1287, 1256, 969, 737 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₂H₁₉N₄ [M+H]⁺: 219.1604, found: 219.1600

Cyclization of **78**. Synthesis of *rac*-2-[(1*R*,2*S*)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)cyclopentyl]acetonitrile (**80**).

A solution compound of **78** (90 mg, 0.44 mmol) in dry DMF (15 mL) was heated in a microwave reactor at 140°C for 1 hour. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude reaction was then purified by column chromatography (silica gel, gradient from CH₂Cl₂ to 98:2 CH₂Cl₂/MeOH) to afford compound **80** (72 mg, 93%) as a yellow oil.



¹H-NMR (400 MHz, CDCl₃): δ 3.80 (m, 2H, 2H-2'), 2.57-2.41 (m, 6H, H-2, H-1, 2H-4' and 2CH₂CN), 2.04 (m, 2H, H-5α and H-3α), 1.87 (m, 2H, 2H-3'), 1.74 (m, 2H, 2H-4), 1.59 (m, 1H, H-3β), 1.51 (m, 1H, H-5β).

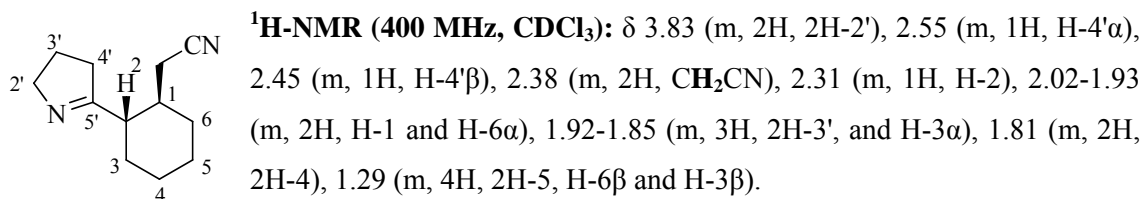
¹³C-NMR (100 MHz, CDCl₃): δ 178.8 (C=N), 119.1 (CN), 60.8 (C-2'), 48.6 (C-2), 39.2 (C-1), 36.3 (C-4'), 31.6 (C-5), 31.0 (C-3), 23.8 (C-4), 22.6 (C-3'), 21.7 (CH₂CN).

FTIR (neat) v_{max}: 2954, 2871, 2247, 1638, 1451, 1424, 1296, 1089, 1021, 971 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₁H₁₇N₂ [M+H]⁺: 177.1386, found: 177.1393

Cyclization of **79**. Synthesis of *rac*-2-[(1*R*,2*S*)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)cyclohexyl]acetonitrile (**81**).

A solution compound of **79** (70 mg, 0.32 mmol) in dry DMF (12 mL) was heated in a microwave reactor at 140°C for 1 hour. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude reaction was then purified by column chromatography (silica gel, gradient from CH₂Cl₂ to 98:2 CH₂Cl₂/MeOH) to afford compound **81** (49 mg, 80%) as a yellow oil.



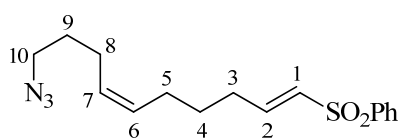
¹³C-NMR (100 MHz, CDCl₃): δ 180.1 (C=N), 119.0 (CN), 60.7 (C-2'), 46.6 (C-2), 36.4 (C-1), 35.8 (C-4'), 31.9 (C-6), 30.9 (C-3), 25.7 (2C, C-5 and C-4), 22.7 (CH₂CN), 22.3 (C-3').

FTIR (neat) v_{max}: 2929, 2857, 2244, 1637, 1449, 1425, 1321, 1017, 977 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₂H₁₉N₂ [M+H]⁺: 191.1543, found: 191.1541

Synthesis of {(1*E*,6*Z*)-10-azidodeca-1,6-dien-1-yl)sulfonyl}benzene (**82**).

To a solution of methyl phenyl sulfone (156 mg, 1.0 mmol) in dry THF (20 mL), cooled at -78°C, *n*-BuLi (0.7 mL, 1.1 mmol, 1.6 M in hexane) was added. The solution was stirred for 30 minutes and a solution of aldehyde **61** (200 mg, 1.1 mmol) in dry THF (10 mL) was added dropwise at -78°C. The resulting solution was stirred for 1 hour at -78°C and then warmed to room temperature over 2 hours. The reaction was quenched with a saturated solution of NH₄Cl and extracted with EtOAc (3 X 30 mL). The organic layer was separated, dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was then dissolved in CH₂Cl₂ (20 mL) at 0°C and methanesulfonyl chloride (0.12 mL, 1.50 mmol) was added. In 15 minutes Et₃N (1.4 mL, 10.0 mmol) was added. The reaction mixture was stirred for 30 minutes at 0°C and then 2 hours at room temperature. After quenching with saturated NH₄Cl solution the contents were extracted with CH₂Cl₂ (3 X 30 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) to afford **82** as a colorless oil (198 mg, 62%, 2 steps).



¹H-NMR (300 MHz, CDCl₃): δ 7.87 (m, 2H, Ar-H), 7.59 (m, 1H, Ar-H), 7.53 (m, 2H, Ar-H), 6.98 (dt, 1H, $J_{2,1} = 15.1$, $J_{2,3} = 6.8$ Hz, H-2), 6.31 (dt, 1H, $J_{1,2} = 15.1$, $J_{1,3} = 1.6$ Hz, H-1), 5.35 (m, 2H, H-7 and H-6), 3.24 (t, 2H, $J_{10,9} = 6.8$ Hz, 2H-10), 2.24 (m, 2H, 2H-3), 2.06 (m, 4H, 2H-5 and 2H-8), 1.61 (m, 2H, 2H-9), 1.52 (m, 2H, 2H-4).

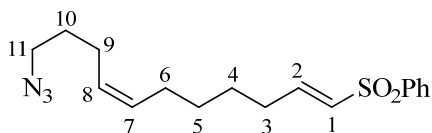
¹³C-NMR (75 MHz, CDCl₃): δ 146.9 (C-2), 140.8 (Ar-C), 133.4 (Ar-C), 130.8 (C-1), 129.9 (C-6), 129.4 (2C, Ar-C), 129.2 (C-7), 127.7 (2C, Ar-C), 50.9 (C-10), 31.1 (C-3), 28.7 (C-9), 27.6 (C-4), 26.6 (C-5), 24.4 (C-8).

FTIR (neat) ν_{max} : 3007, 2935, 2862, 2097, 1626, 1447, 1318, 1307, 1289, 1255, 1146, 1087, 968, 817, 753 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₆H₂₂N₃O₂S [M+H]⁺: 320.1427, found: 320.1418

Synthesis of [(1E,7Z)-11-azidoundeca-1,7-dien-1-yl]sulfonylbenzene (**83**).

To a solution of methyl phenyl sulfone (145 mg, 0.93 mmol) in THF (20 mL), cooled at -78°C, n-BuLi (0.64 mL, 1.6 M in hexane, 1.02 mmol) was added. The solution was stirred for 30 minutes and a solution of **66** (200 mg, 1.02 mmol) in THF (10 mL) was added at -78°C. The resulting solution was stirred for 1 hour at -78°C and then 2 hours at room temperature. The reaction mixture was quenched with a saturated solution of NH₄Cl (15 mL) and extracted with EtOAc (3 X 30 mL). The organic layer was dried with MgSO₄, filtered and concentrated in vacuo. The crude alcohol was dissolved in CH₂Cl₂ (15 mL) at 0°C. Et₃N (1.3 mL, 9.3 mmol) and methanesulfonyl chloride (0.1 mL, 1.39 mmol) were added. After the mixture was stirred for 2 hours at room temperature a saturated solution of NH₄Cl (15 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (3 X 30 mL) and the combined organic layers were dried with MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) yielded compound **83** as a colorless oil (210 mg, 68%, 2 steps).



¹H-NMR (300 MHz, CDCl₃): δ 7.88 (m, 2H, Ar-H), 7.60 (m, 1H, Ar-H), 7.54 (m, 2H, Ar-H), 6.99 (dt, 1H, $J_{2,1} = 15.0$, $J_{2,3} = 6.9$ Hz, H-2), 6.31 (dt, 1H, $J_{1,2} = 15.0$, $J_{1,3} = 1.5$ Hz, H-1), 5.34 (m, 2H, H-7 and H-8), 3.26 (t, 2H, $J_{11,10} = 6.8$ Hz, 2H-11), 2.24 (m, 2H, 2H-3), 2.107 (m, 4H, 2H-9 and 2H-6), 1.64 (m, 2H, 2H-10), 1.47 (m, 2H, 2H-4), 1.36 (m, 2H, 2H-5).

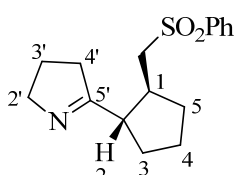
^{13}C -NMR (75 MHz, CDCl_3): δ 147.1 (C-2), 140.9 (Ar-C), 133.4 (Ar-C), 130.7 (C-7), 130.6 (C-1), 129.4 (2C, Ar-C), 128.6 (C-8), 127.7 (2C, Ar-C), 50.9 (C-11), 31.5 (C-3), 29.1 (C-5), 28.8 (C-10), 27.3 (C-4), 26.9 (C-6), 24.4 (C-9).

FTIR (neat) ν_{max} : 2933, 2859, 2096, 1626, 1447, 1319, 1307, 1290, 1147, 1087, 971, 821, 752, 688 cm^{-1} .

HRMS-ESI (m/z): for $\text{C}_{34}\text{H}_{46}\text{N}_6\text{NaO}_4\text{S}_2$ $[\text{2M}+\text{Na}]^+$: 689.2920, found: 689.2912

Cyclization of 82. Synthesis of *rac*-5-[(1*S*,2*S*)-2-[(phenylsulfonyl)methyl]cyclopentyl]-3,4-dihydro-2*H*-pyrrole (84).

A solution compound of **82** (60 mg, 0.19 mmol) in dry DMF (8 mL) was heated in a microwave reactor at 140°C for 1 hour. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude reaction was then purified by column chromatography (silica gel, gradient from CH_2Cl_2 to 98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford compound **84** (53 mg, 96%) as a yellow oil.



^1H -NMR (400 MHz, CDCl_3): δ 7.88 (m, 2H, Ar-H), 7.63 (m, 1H, Ar-H), 7.54 (m, 2H, Ar-H), 3.73 (m, 2H, 2H-2'), 3.35 (dd, 1H, $J = 14.1$, $J = 3.4$ Hz, $\text{CH}_2\text{SO}_2\text{Ph}$), 3.01 (dd, 1H, $J = 14.1$, $J = 9.6$ Hz, $\text{CH}_2\text{SO}_2\text{Ph}$), 2.53 (m, 1H, H-2), 2.45-2.28 (m, 3H, 2H-4' and H-1), 2.12 (m, 1H, H-5 α), 1.93-1.66 (m, 5H, H-3 α , 2H-3' and 2H-4), 1.58 (m, 1H, H-3 β), 1.40 (m, 1H, H-5 β).

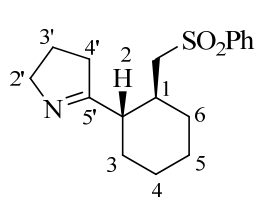
^{13}C -NMR (100 MHz, CDCl_3): δ 179.0 (C=N), 139.9 (Ar-C), 133.7 (Ar-C), 129.3 (2C, Ar-C), 128.0 (2C, Ar-C), 60.7 (C-2'), 60.6 ($\text{CH}_2\text{SO}_2\text{Ph}$), 49.9 (C-2), 38.0 (C-1), 34.6 (C-4'), 32.3 (C-5), 29.7 (C-3), 24.3 (C-4), 22.5 (C-3').

FTIR (neat) ν_{max} : 3419, 2958, 2871, 1637, 1447, 1304, 1147, 1086, 747, 690 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 292.1366, found: 292.1375

Cyclization of 83. Synthesis of *rac*-5-[(1*S*,2*S*)-2-[(phenylsulfonyl)methyl]cyclohexyl]-3,4-dihydro-2*H*-pyrrole (85).

A solution compound **83** (80 mg, 0.24 mmol) in dry toluene (8 mL) was heated in a microwave reactor at 120°C for 2 hour. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude reaction was then purified by column chromatography (silica gel, gradient from CH_2Cl_2 to 98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford compound **85** (66 mg, 90%) as a pale yellow oil.



$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.84 (m, 2H, Ar-H), 7.62 (m, 1H, Ar-H), 7.54 (m, 2H, Ar-H), 3.70 (m, 2H, 2H-2'), 3.14 (dd, 1H, $J = 14.4$, $J = 1.8$ Hz, $\text{CH}_2\text{SO}_2\text{Ph}$), 2.86 (dd, 1H, $J = 14.4$, $J = 8.9$ Hz, $\text{CH}_2\text{SO}_2\text{Ph}$), 2.28 (m, 4H, 2H-4', H-2 and H-6 α), 2.09 (m, 1H, H-1), 1.82-1.68 (m, 5H, 2H-3', 2H-4, H-3 α), 1.36 (m, 1H, H-3 β), 1.27 (m, 2H, 2H-5), 1.15 (m, 1H, H-6 β).

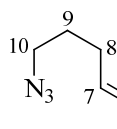
$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 180.2 (C=N), 140.2 (Ar-C), 133.7 (Ar-C), 129.3 (2C, Ar-C), 127.9 (2C, Ar-C), 60.4 (C-2'), 60.1 ($\text{CH}_2\text{SO}_2\text{Ph}$), 47.6 (C-2), 34.6 (C-1), 33.7 (C-4'), 33.0 (C-6), 30.6 (C-3), 25.7 (C-4), 25.3 (C-5), 22.5 (C-3').

FTIR (neat) ν_{max} : 3411, 2929, 2858, 1635, 1447, 1304, 1145, 1086, 814, 787, 746, 690 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 306.1522, found: 306.1522

Synthesis of diethyl [(1*E*,6*Z*)-10-azidodeca-1,6-dien-1-yl]phosphonate (**86**).

Tetraethylmethylene diphosphonate (476 mg, 1.65 mmol) in dry THF (5 mL) was added to a suspension of NaH (66 mg, 1.65 mmol) in dry THF (15 mL) at 0°C. After 30 minutes a solution of aldehyde **61** (200 mg, 1.10 mmol) in THF (10 mL) was added dropwise and the reaction mixture was stirred at 0°C for 40 minutes. The reaction was warmed to room temperature and then quenched with saturated NH_4Cl . The mixture was extracted with EtOAc (3 X 30 mL) and the organic layer was dried with MgSO_4 , filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography (silica gel, gradient from hexanes to 60:40 hexanes/EtOAc) to obtain compound **86** as a colorless oil (295 mg, 85%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 6.75 (ddt, 1H, $J_{2,\text{P}} = 22.0$, $J_{2,1} = 17.1$, $J_{2,3} = 6.5$ Hz, H-2), 5.64 (ddt, 1H, $J_{1,\text{P}} = 20.8$, $J_{1,2} = 17.1$, $J_{1,3} = 1.5$ Hz, H-1), 5.36 (m, 2H, H-6 and H-7), 4.05 (m, 4H, $\text{PO}(\text{OCH}_2\text{CH}_3)_2$), 3.25 (t, 2H, $J_{10,9} = 6.8$ Hz, 2H-10), 2.21 (m, 2H, 2H-3), 2.07 (m, 4H, 2H-8 and 2H-5), 1.62 (m, 2H, 2H-9), 1.51 (m, 2H, 2H-4), 1.30 (t, 6H, $J = 7.1$ Hz, $\text{PO}(\text{OCH}_2\text{CH}_3)_2$).

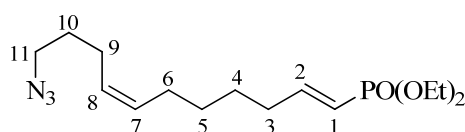
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 153.5 (d, $J_{\text{C,P}} = 4$ Hz, C-2), 130.5 (C-6), 128.9 (C-7), 117.3 (d, $J_{\text{C,P}} = 188$ Hz, C-1), 61.7 (2C, d, $J_{\text{C,P}} = 5$ Hz, $\text{PO}(\text{OCH}_2\text{CH}_3)_2$), 51.0 (C-10), 33.8 (d, $J_{\text{C,P}} = 22$ Hz, C-3), 28.8 (C-9), 27.9 (C-4), 26.7 (C-5), 24.4 (C-8), 16.5 (2C, d, $J_{\text{C,P}} = 6$ Hz, $\text{PO}(\text{OCH}_2\text{CH}_3)_2$).

FTIR (neat) ν_{max} : 3467, 2982, 2933, 2864, 2097, 1632, 1445, 1392, 1368, 1347, 1250, 1055, 1028, 963 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{14}\text{H}_{27}\text{N}_3\text{O}_3\text{P}$ $[\text{M}+\text{H}]^+$: 316.1785, found: 316.1782

Synthesis of diethyl [(1*E*,7*Z*)-11-azidoundeca-1,7-dien-1-yl]phosphonate (87**).**

Tetraethylmethylenediphosphonate (441 mg, 1.53 mmol) in dry THF (5 mL) was added to a suspension of NaH (61 mg, 1.53 mmol) in dry THF (15 mL) at 0°C. After 30 minutes a solution of aldehyde **66** (200 mg, 1.02 mmol) in THF (10 mL) was added dropwise and the reaction mixture was stirred at 0°C for 40 minutes. The reaction was warmed to room temperature and then quenched with saturated NH₄Cl. The mixture was extracted with EtOAc (3 X 30 mL) and the organic layer was dried with MgSO₄, filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography (silica gel, gradient from hexanes to 60:40 hexanes/EtOAc) to obtain compound **87** as a colorless oil (312 mg, 93%).



¹H-NMR (300 MHz, CDCl₃): δ 6.77 (ddt, 1H, $J_{2,P} = 22.0$, $J_{2,1} = 17.1$, $J_{2,3} = 6.6$ Hz, H-2), 5.64 (ddt, 1H, $J_{1,P} = 21.0$, $J_{1,2} = 17.1$, $J_{1,3} = 1.5$ Hz, H-1), 5.36 (m, 2H, H-8 and H-7), 4.05 (m, 4H, PO(OCH₂CH₃)₂), 3.27 (t, 2H, $J_{11,10} = 6.8$ Hz, 2H-11), 2.22 (m, 2H, 2H-3), 2.17-1.99 (m, 4H, 2H-9 and 2H-6), 1.64 (m, 2H, 2H-10), 1.46-1.38 (m, 4H, 2H-4 and 2H-5), 1.32 (t, 6H, $J = 7.1$ Hz, PO(OCH₂CH₃)₂).

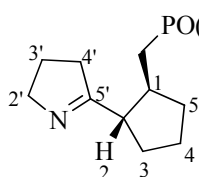
¹³C-NMR (75 MHz, CDCl₃): δ 153.8 (d, $J_{C,P} = 4$ Hz, C-2), 130.9 (C-7), 128.4 (C-8), 117.0 (d, $J_{C,P} = 188$ Hz, C-1), 61.7 (2C, d, $J_{C,P} = 6$ Hz, PO(OCH₂CH₃)₂), 51.0 (C-11), 34.2 (d, $J_{C,P} = 22$ Hz, C-3), 29.2 (C-5), 28.9 (C-10), 27.5 (C-4), 27.0 (C-6), 24.4 (C-9), 16.5 (2C, d, $J_{C,P} = 6$ Hz, PO(OCH₂CH₃)₂).

FTIR (neat) ν_{\max} : 2982, 2932, 2859, 2097, 1632, 1445, 1392, 1367, 1347, 1249, 1165, 1056, 1029, 963, 839 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₅H₂₉N₃O₃P [M+H]⁺: 330.1947, found: 330.1962

Cyclization of **86. Synthesis of *rac*-diethyl [(1*S*,2*S*)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)cyclopentyl]methyl]phosphonate (**88**).**

A solution of compound **86** (64 mg, 0.20 mmol) in dry DMF (8 mL) was heated in a microwave reactor at 140°C for 8 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude reaction was then purified by column chromatography (silica gel, gradient from CH₂Cl₂ to 97:3 CH₂Cl₂/MeOH) to afford compound **88** (50 mg, 87%) as a yellow oil.



¹H-NMR (400 MHz, CDCl₃): δ 4.05 (m, 4H, PO(OCH₂CH₃)₂), 3.77 (m, 2H, 2H-2'), 2.64-2.41 (m, 3H, 2H-4' and H-2), 2.22 (m, 1H, H-1), 2.12 (m, 1H, H-5α), 1.95-1.79 (m, 4H, 2H-3', H-3α and CH₂PO(OEt)₂),

1.69 (m, 2H, 2H-4), 1.60 (m, 2H, H-3 β and CH₂PO(OEt)₂), 1.35 (m, 1H, H-5 β), 1.29 (t, 6H, J = 7.0 Hz, PO(OCH₂CH₃)₂).

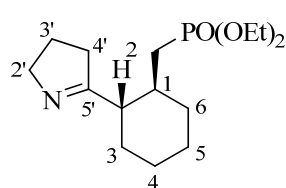
¹³C-NMR (100 MHz, CDCl₃): δ 180.1 (C=N), 61.6 (C-2'), 60.5 (2C, d, $J_{C,P}$ = 9 Hz, PO(OCH₂CH₃)₂), 51.4 (d, $J_{C,P}$ = 17 Hz, C-2), 38.4 (d, $J_{C,P}$ = 4 Hz, C-1), 34.5 (C-4'), 33.1 (C-5), 30.9 (d, $J_{C,P}$ = 23 Hz, CH₂PO(OEt)₂), 30.0 (C-3), 29.4 (C-4), 22.5 (C-3'), 16.5 (2C, d, $J_{C,P}$ = 6 Hz, PO(OCH₂CH₃)₂).

FTIR (neat) ν_{\max} : 3435, 2959, 2872, 1639, 1449, 1393, 1224, 1054, 1027, 967 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₄H₂₇NO₃P [M+H]⁺: 288.1723, found: 288.1633

Cyclization of **87**. Synthesis of *rac*-diethyl [(1*S*,2*S*)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)cyclohexyl]methyl}phosphonate (**89**).

A solution of compound **87** (65 mg, 0.20 mmol) in dry DMF (8 mL) was heated in a microwave reactor at 140°C for 8 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude reaction was then purified by column chromatography (silica gel, gradient from CH₂Cl₂ to 98:2 CH₂Cl₂/MeOH) to afford compound **89** (54 mg, 91%) as a yellow oil.



¹H-NMR (400 MHz, CDCl₃): δ 4.03 (m, 4H, PO(OCH₂CH₃)₂), 3.76 (m, 2H, 2H-2'), 2.43 (m, 2H, 2H-4'), 2.23 (m, 2H, H-2 and H-6 α), 1.90 (m, 1H, H-1), 1.82 (m, 2H, 2H-3'), 1.72 (m, 4H, 2H-4, H-3 α and CH₂PO(OEt)₂), 1.51-1.39 (m, 2H, H-3 β and CH₂PO(OEt)₂), 1.29 (m, 2H, 2H-5), 1.28 (t, 6H, J = 7.1 Hz, PO(OCH₂CH₃)₂), 1.06 (m, 1H, H-6 β).

¹³C-NMR (100 MHz, CDCl₃): δ 181.0 (C=N), 61.4 (2C, d, $J_{C,P}$ = 6 Hz, PO(OCH₂CH₃)₂), 60.4 (C-2'), 49.5 (d, $J_{C,P}$ = 17 Hz, C-2), 34.7 d, $J_{C,P}$ = 4 Hz, (C-1), 33.9 (C-4'), 33.1 (C-6), 31.0 (d, $J_{C,P}$ = 15 Hz, CH₂PO(OEt)₂), 29.7 (C-3), 26.0 (C-5), 25.6 (C-4), 22.5 (C-3'), 16.5 (2C, d, $J_{C,P}$ = 6 Hz, PO(OCH₂CH₃)₂).

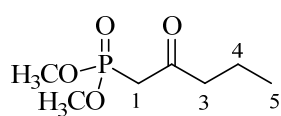
FTIR (neat) ν_{\max} : 3469, 2980, 2929, 2858, 1665, 1637, 1448, 1391, 1231, 1051, 1027, 962, 820 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₅H₂₉NO₃P [M+H]⁺: 302.1880, found: 302.1883

Synthesis of dimethyl (2-oxopentyl)phosphonate (**90**).

A 1.6M solution of n-BuLi in hexanes (61 mL, 98 mmol) was added dropwise to a solution of dimethyl methylphosphonate (13 mL, 118 mmol) in THF (40 mL) at -78°C. After

stirring for 30 minutes, methyl butyrate (5 g, 49 mmol) in THF (15 mL) was added over 20 minutes. The mixture was stirred for an additional 2 hours and then it was quenched with saturated solution of NH_4Cl . The solution was warmed to room temperature and extracted with EtOAc (3 X 50 mL). The organic layers were washed with brine, dried over MgSO_4 and concentrated in vacuo. The resulting oil was purified by column chromatography (silica gel, gradient from 1:1 hexanes/EtOAc to 95:5 EtOAc/MeOH) to obtain compound **90** as a colorless oil (7.99 g, 84%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 3.75 (d, 6H, $J_{\text{CH}_3,\text{P}} = 11.2$ Hz, OCH_3), 3.05 (dd, 2H, $J_{1,\text{P}} = 22.8$ Hz, 2H-1), 2.57 (t, 2H, $J_{3,4} = 7.2$ Hz, 2H-3), 1.59 (m, 2H, 2H-4), 0.89 (t, 3H, $J_{5,4} = 7.4$ Hz, 3H-5).

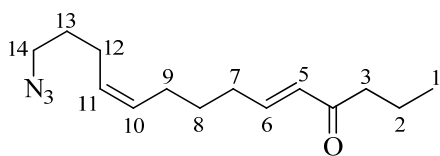
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 202.0 (d, $J_{\text{C,P}} = 6$ Hz, C=O), 53.1 (2C, d, $J_{\text{C,P}} = 7$ Hz, OCH_3), 46.1 (C-3), 41.4 (d, $J_{\text{C,P}} = 128$ Hz, C-1), 16.9 (C-4), 13.5 (C-5).

FTIR (neat) ν_{max} : 3469, 2962, 1714, 1258, 1230, 811 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_7\text{H}_{16}\text{O}_4\text{P}$ $[\text{M}+\text{H}]^+$: 195.0781, found: 195.0780

Synthesis of (5E,10Z)-14-azidotetradeca-5,10-dien-4-one (**91**).

A suspension of NaH (132 mg of 60% in mineral oil, 3.30 mmol) in dry THF (25 mL) was cooled to -78°C . Dimethyl (2-oxopentyl)phosphonate (compound **90**, 641 mg, 3.30 mmol) was added dropwise and the reaction mixture was stirred for 20 minutes at -78°C and 20 minutes at 0°C . Then a solution of **61** (300 mg, 1.65 mmol) in dry THF (10 mL) was added dropwise and the mixture was stirred for 30 minutes at 0°C . The reaction was warmed to room temperature and after 1 hour and 30 minutes it was quenched with water and extracted with Et_2O (3 X 30 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) yielded compound **91** as a colorless oil (288 mg, 70%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 6.82 (dt, 1H, $J_{6,5} = 15.9$, $J_{6,7} = 6.9$ Hz, H-6), 6.09 (dt, 1H, $J_{5,6} = 15.9$, $J_{5,7} = 1.6$ Hz, H-5), 5.38 (m, 2H, H-10 and H-11), 3.27 (t, 2H, $J_{14,13} = 6.8$ Hz, 2H-14), 2.51 (t, 2H, $J_{3,2} = 7.3$ Hz, 2H-3), 2.22 (m, 2H, 2H-7), 2.10 (m, 4H, 2H-12 and 2H-9), 1.64 (m, 4H, 2H-2 and 2H-13), 1.54 (m, 2H, 2H-8), 0.93 (t, 3H, $J_{1,2} = 7.4$ Hz, CH_3).

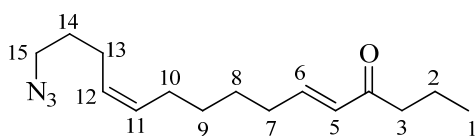
^{13}C -NMR (75 MHz, CDCl_3): δ 210.3 (C=O), 147.3 (C-6), 131.1 (C-5), 130.9 (C-10), 129.3 (C-11), 51.4 (C-14), 32.5 (C-3), 29.2 (C-7), 28.6 (C-13 and C-8), 27.2 (C-9), 24.9 (C-12), 18.3 (C-2), 14.4 (C-1).

FTIR (neat) ν_{max} : 3007, 2961, 2934, 2874, 2096, 1696, 1674, 1630, 1456, 1366, 1347, 1285, 1257, 1197, 978 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{14}\text{H}_{24}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 250.1914, found: 250.1916

Synthesis of (5E,11Z)-15-azidopentadeca-5,11-dien-4-one (92).

A suspension of NaH (129 mg of 60% in mineral oil, 3.22 mmol) in dry THF (25 mL) was cooled to -78°C . Dimethyl (2-oxopentyl)phosphonate (compound **90**, 625 mg, 3.22 mmol) dissolved in THF (15 mL) was added dropwise and the reaction mixture was stirred for 20 minutes at -78°C and 20 minutes at 0°C . Then a solution of **66** (420 mg, 2.15 mmol) in dry THF (15 mL) was added dropwise and the mixture was stirred for 30 minutes at 0°C . The reaction was warmed to room temperature and after 1 hour and 30 minutes it was quenched with water and extracted with Et_2O (3 X 30 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) yielded compound **92** as a colorless oil (470 mg, 83%).



^1H -NMR (300 MHz, CDCl_3): δ 6.81 (dt, 1H, $J_{6,5} = 15.9$, $J_{6,7} = 6.9$ Hz, H-6), 6.09 (dt, 1H, $J_{5,6} = 15.9$, $J_{5,7} = 1.5$ Hz, H-5), 5.38 (m, 2H, H-11 and H-12), 3.27 (t, 2H, $J_{15,14} = 6.8$ Hz, 2H-15), 2.50 (t, 2H, $J_{3,2} = 7.3$ Hz, 2H-3), 2.21 (m, 2H, 2H-7), 2.17-2.01 (m, 4H, 2H-10 and 2H-13), 1.71-1.57 (m, 4H, 2H-2 and 2H-14), 1.47 (m, 2H, 2H-8), 1.38 (m, 2H, 2H-9), 0.93 (t, 3H, $J_{1,2} = 7.4$ Hz, CH_3).

^{13}C -NMR (75 MHz, CDCl_3): δ 200.9 (C=O), 147.1 (C-6), 130.9 (C-11), 130.6 (C-5), 128.4 (C-12), 51.0 (C-15), 42.2 (C-3), 32.4 (C-7), 29.3 (C-9), 28.9 (C-14), 27.9 (C-8), 27.1 (C-10), 24.4 (C-13), 17.9 (C-2), 14.0 (C-1).

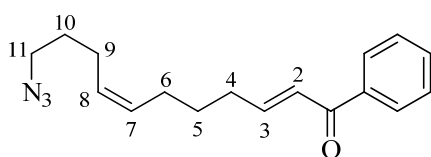
FTIR (neat) ν_{max} : 3006, 2934, 2867, 2096, 1672, 1453, 1285, 979 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{15}\text{H}_{26}\text{NO}$ $[\text{M}+\text{H}-\text{N}_2]^+$: 236.2014, found: 236.2069

Synthesis of (2E,7Z)-11-azido-1-phenylundeca-2,7-dien-1-one (93).

To a solution of **61** (200 mg, 1.1 mmol) in CH_2Cl_2 (20 mL) was added 1-phenyl-2-(triphenylphosphoranylidene)ethanone (1255 mg, 3.3 mmol) at room temperature and the

mixture was stirred for 4 days. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) to provide compound **93** as a colorless oil (290 mg, 93%).



¹H-NMR (300 MHz, CDCl₃): δ 7.93 (m, 2H, Ar-H), 7.55 (m, 1H, Ar-H), 7.46 (m, 2H, Ar-H), 7.06 (dt, 1H, $J_{3,2} = 15.4$, $J_{3,4} = 6.8$ Hz, H-3), 6.89 (dt, 1H, $J_{2,3} = 15.4$, $J_{2,4} = 1.4$ Hz, H-2), 5.41 (m, 2H, H-7 and H-8), 3.27 (t, 2H, $J_{11,10} = 6.8$ Hz, 2H-11), 2.34 (m, 2H, 2H-4), 2.11 (m, 4H, 2H-6 and 2H-9), 1.62 (m, 4H, 2H-5 and 2H-10).

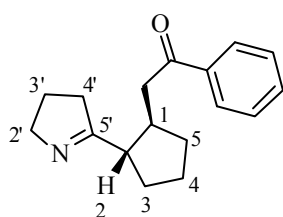
¹³C-NMR (75 MHz, CDCl₃): δ 191.0 (C=O), 149.6 (C-3), 138.1 (Ar-C), 132.7 (Ar-C), 130.4 (C-7), 128.9 (C-8), 128.6 (4C, Ar-C), 126.3 (C-2), 51.0 (C-11), 32.5 (C-4), 28.8 (C-10), 28.3 (C-5), 26.9 (C-6), 24.5 (C-9).

FTIR (neat) ν_{\max} : 2933, 2861, 2096, 1671, 1621, 1448, 1284, 694 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₇H₂₂N₃O [M+H]⁺: 284.1757, found: 284.1753

Cyclization of **93**. Synthesis of *rac*-2-[(1*R*,2*S*)-2-(3,4-dihydro-2*H*-pyrrol-5-yl)cyclopentyl]-1-phenylethanone (**94**).

A solution compound of **93** (80 mg, 0.28 mmol) in dry DMF (9 mL) was heated in a microwave reactor at 140°C for 2 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude reaction was then purified by column chromatography (silica gel, gradient from CH₂Cl₂ to 98:2 CH₂Cl₂/MeOH) to afford compound **94** (14 mg, 20%) as a yellow oil.



¹H-NMR (500 MHz, CDCl₃): δ 7.94 (m, 2H, Ar-H), 7.52 (m, 1H, Ar-H), 7.43 (m, 2H, Ar-H), 3.73 (m, 2H, 2H-2'), 3.18 (dd, 1H, $J = 16.6$, $J = 4.1$ Hz, CH₂COPh), 2.88 (dd, 1H, $J = 16.6$, $J = 8.5$ Hz, CH₂COPh), 2.63-2.41 (m, 4H, H-1, H-2 and 2H-4'), 2.07 (m, 1H, H-5 α), 1.93 (m, 1H, H-3 α), 1.82 (m, 2H, 2H-3'), 1.76-1.61 (m, 3H, H-3 β and 2H-4), 1.26 (m, 1H, H-5 β).

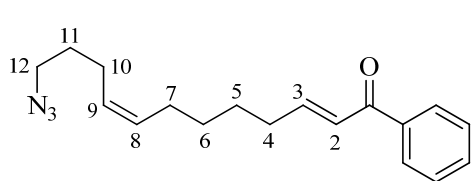
¹³C-NMR (125 MHz, CDCl₃): δ 200.1 (C=O), 180.3 (C=N), 137.2 (Ar-C), 133.0 (Ar-C), 128.6 (2C, Ar-C), 128.2 (2C, Ar-C), 60.6 (C-2'), 50.3 (C-2), 43.7 (CH₂COPH), 39.8 (C-1), 34.5 (C-4'), 32.6 (C-5), 30.4 (C-3), 24.2 (C-4), 22.6 (C-3').

FTIR (neat) ν_{\max} : 3252, 2949, 2867, 1683, 1635, 1597, 1578, 1448, 1372, 1278, 1212, 987, 754, 692 cm⁻¹.

HRMS-ESI (m/z): calcd for $C_{17}H_{22}NO$ $[M+H]^+$: 256.1696, found: 288.1685

Synthesis of (2E,8Z)-12-azido-1-phenyldodeca-2,8-dien-1-one (95).

To a solution of **66** (200 mg, 1.02 mmol) in CH_2Cl_2 (20 mL) was added 1-phenyl-2-(triphenylphosphoranylidene)ethanone (1164 mg, 3.06 mmol) at room temperature and the mixture was stirred for 4 days. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) to provide compound **95** as a colorless oil (279 mg, 92%).



1H -NMR (300 MHz, $CDCl_3$): δ 7.90 (m, 2H, Ar-H), 7.50 (m, 1H, Ar-H), 7.43 (m, 2H, Ar-H), 7.04 (dt, 1H, $J_{3,2} = 15.4$, $J_{3,4} = 6.8$ Hz, H-3), 6.86 (dt, 1H, $J_{2,3} = 15.4$, $J_{2,4} = 1.3$ Hz, H-2), 5.35 (m, 2H, H-8 and H-9),

3.23 (t, 2H, $J_{12,11} = 6.8$ Hz, 2H-12), 2.29 (m, 2H, 2H-4), 2.07 (m, 4H, 2H-7 and 2H-10), 1.61 (m, 2H, 2H-11), 1.51 (m, 2H, 2H-5), 1.40 (m, 2H, 2H-6).

^{13}C -NMR (75 MHz, $CDCl_3$): δ 190.7 (C=O), 149.4 (C-3), 138.2 (Ar-C), 132.4 (Ar-C), 130.8 (C-8), 128.5 (4C, Ar-C), 128.3 (C-9), 126.3 (C-2), 50.9 (C-12), 32.6 (C-4), 29.2 (C-6), 28.8 (C-11), 27.9 (C-5), 27.0 (C-7), 24.4 (C-10).

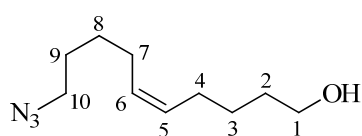
FTIR (neat) ν_{max} : 3435, 2933, 2095, 1668, 1650, 1623, 1226, 978 cm^{-1} .

HRMS-ESI (m/z): calcd for $C_{18}H_{24}N_3O$ $[M+H]^+$: 298.1914, found: 198.1922

2.3.3.2.- Synthesis of no fused bicyclic piperideines.

Wittig reaction. Synthesis of (Z)-10-azidodec-5-en-1-ol (96).

Phosphonium salt **6** (4.00 g, 8.82 mmol) was dissolved in dry CH_2Cl_2 (5 mL). THF (45 mL) was added and the solution was cooled to $-78^\circ C$. Then KHMDS (17.6 mL, 8.82 mmol, 0.5 M solution in toluene) was added. After the reaction mixture was stirred for 30 minutes at $-78^\circ C$, a solution of aldehyde **59** (600 mg, 5.88 mmol) in dry THF (30 mL) was added dropwise over 25 minutes. After 50 minutes, the reaction mixture was warmed to room temperature over 2 hours. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) provided compound **96** as a colorless oil (649 mg, 56%).



¹H-NMR (300 MHz, CDCl₃): δ 5.37 (m, 2H, H-5 and H-6), 3.64 (t, 2H, $J_{1,2} = 6.4$ Hz, 2H-1), 3.26 (t, 2H, $J_{10,9} = 6.9$ Hz, 2H-10), 2.06 (m, 4H, 2H-4 and 2H-7), 1.59 (m, 4H, 2H-2 and 2H-9), 1.43 (m, 4H, 2H-3 and 2H-8).

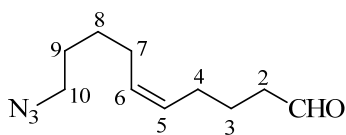
¹³C-NMR (75 MHz, CDCl₃): δ 130.3 (C-6), 129.5 (C-5), 63.0 (C-1), 51.5 (C-10), 32.5 (C-2), 28.6 (C-9), 27.1 (C-4), 26.9 (C-7), 26.8 (C-8), 25.9 (C-3).

FTIR (neat) ν_{\max} : 3339, 2935, 2862, 2097, 1456, 1248, 1062 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₀H₂₀N₃O [M+H]⁺: 198.1601, found: 198.1596

Oxidation of alcohol **96**. Synthesis of (Z)-10-azidodec-5-enal (**97**).

PCC (1225 mg, 5.68 mmol) was added to a solution of **96** (560 mg, 2.84 mmol) in CH₂Cl₂ (30 mL) at room temperature. The mixture was stirred for 2 hours and then it was filtered through a plug of Celite. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) provided compound **97** as a colorless oil (443 mg, 80%).



¹H-NMR (300 MHz, CDCl₃): δ 9.77 (s, 1H, CHO), 5.37 (m, 2H, H-5 and H-6), 3.26 (t, 2H, $J_{10,9} = 6.8$ Hz, 2H-10), 2.44 (td, 2H, $J_{2,3} = 7.3$, $J = 1.6$ Hz, 2H-2), 2.06 (m, 4H, 2H-7 y 2H-4), 1.69 (m, 2H, 2H-3), 1.60 (m, 2H, 2H-9), 1.43 (m, 2H, 2H-8).

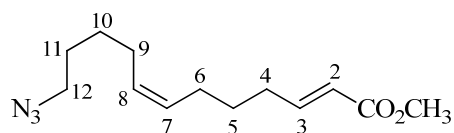
¹³C-NMR (75 MHz, CDCl₃): δ 202.6 (CHO), 130.4 (C-6), 129.2 (C-5), 51.5 (C-10), 43.4 (C-2), 28.6 (C-9), 26.8 (2C, C-8 and C-7), 26.6 (C-4), 22.1 (C-3).

FTIR (neat) ν_{\max} : 2937, 2863, 2097, 1725, 1456, 1248, 1069 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₀H₁₈NO [M+H-N₂]⁺: 168.1388, found: 168.1386

Synthesis of (2E,7Z)-methyl 12-azidododeca-2,7-dienoate (**98**).

To a solution of **97** (200 mg, 1.02 mmol) in CH₂Cl₂ (30 mL) was added (methoxycarbonylmethylene)triphenylphosphorane (684 mg, 2.04 mmol) at room temperature and the mixture was stirred overnight. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 95:5 hexanes/EtOAc) to provide compound **98** as a colorless oil (251 mg, 98%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 6.96 (dt, 1H, $J_{3,2} = 15.6$, $J_{3,4} = 6.9$ Hz, H-3), 5.82 (dt, 1H, $J_{2,3} = 15.6$, $J_{2,4} = 1.4$ Hz, H-2), 5.36 (m, 2H, H-8 and H-7), 3.72 (s, 3H, CO_2CH_3), 3.26 (t, 2H, $J_{12,11} = 6.8$ Hz, 2H-12), 2.21 (m, 2H, 2H-4), 2.06 (m, 4H, 2H-9 and 2H-6), 1.63-1.39 (m, 6H, 2H-11, 2H-5 and 2H-10).

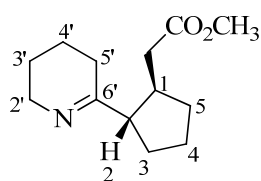
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 167.2 (CO_2CH_3), 149.4 (C-3), 130.0 (C-7), 129.6 (C-8), 121.2 (C-2), 51.5 (2C, CO_2CH_3 , C-12), 31.8 (C-4), 28.6 (C-11), 28.1 (C-5), 26.9 (2C, C-9 and C-6), 26.6 (C-10).

FTIR (neat) ν_{max} : 3006, 2936, 2860, 2096, 1725, 1658, 1456, 1436, 1271, 1202, 1040, 979, 718 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{13}\text{H}_{22}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 252.1707, found: 252.1709

Cyclization of **98**. Synthesis of *rac*-methyl 2-[(1*R*,2*S*)-2-(3,4,5,6-tetrahydropyridin-2-yl)cyclopentyl]acetate (**99**).

A solution of compound **98** (80 mg, 0.31 mmol) in a mixture of DMF/EtOH (10 mL, 4:1) was heated in a microwave reactor at 140°C for 2 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The resulting reaction crude was then purified by column chromatography (silica gel, gradient from CH_2Cl_2 to 97:3 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford compound **99** (44 mg, 63%) as a pale yellow oil.



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 3.63 (s, 3H, CO_2CH_3), 3.56 (m, 2H, 2H-2'), 2.52-2.36 (m, 3H, H-2, H-1 and $\text{CH}_2\text{CO}_2\text{CH}_3$), 2.35-2.25 (m, 2H, $\text{CH}_2\text{CO}_2\text{CH}_3$ and H-5' α), 2.19 (m, 1H, H-5' β), 2.01-1.88 (m, 2H, H-3 α and H-5 α), 1.74-1.55 (m, 7H, 2H-3', 2H-4', 2H-4 and H-3 β), 1.30 (m, 1H, H-5 β).

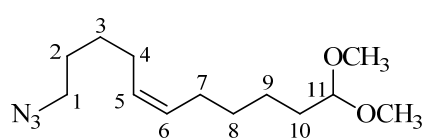
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 173.8 (C=N), 169.1 (C=O), 55.6 (C-2), 51.7 (CO_2CH_3), 48.1 (C-2'), 40.1 (C-1), 38.9 ($\text{CH}_2\text{CO}_2\text{CH}_3$), 32.7 (C-5), 30.9 (C-3), 27.1 (C-5'), 24.3 (C-4), 21.7 (C-3'), 19.3 (C-4').

FTIR (neat) ν_{max} : 2934, 2866, 1738, 1661, 1437, 1329, 1251, 1195, 1176, 921 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{13}\text{H}_{22}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 224.1645, found: 224.1642

Wittig reaction. Synthesis of (Z)-1-azido-11,11-dimethoxyundec-5-ene (100).

Phosphonium salt **6** (4.26 g, 9.37 mmol) was dissolved in dry CH_2Cl_2 (4 mL). THF (36 mL) was added and the solution was cooled to -78°C . Then KHMDs (18.8 mL, 9.37 mmol, 0.5 M solution in toluene) was added. After the reaction mixture was stirred for 30 minutes at -78°C , a solution of aldehyde **64** (1 g, 6.25 mmol) in dry THF (20 mL) was added dropwise over 25 minutes. After 1 hour, the reaction mixture was warmed to room temperature over 2 hours. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) yielded compound **100** as a colorless oil (878 mg, 55%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.36 (m, 2H, H-5 and H-6), 4.35 (t, 1H, $J_{11,10} = 5.7$ Hz, H-11), 3.31 (s, 6H, OCH_3), 3.26 (t, 2H, $J_{1,2} = 6.9$ Hz, 2H-1), 2.04 (m, 4H, 2H-4 and 2H-7), 1.60 (m, 4H, 2H-2 and 2H-10), 1.43 (m, 2H, 2H-8), 1.36 (m, 4H, 2H-9 and 2H-3).

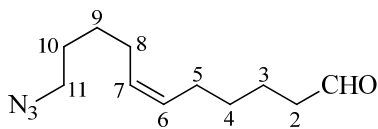
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 130.5 (C-6), 129.2 (C-5), 104.6 (C-11), 52.8 (2C, OCH_3), 51.5 (C-1), 32.5 (C-10), 29.7 (C-3), 28.6 (C-2), 27.3 (C-4), 26.9 (C-8), 26.8 (C-7), 24.4 (C-9).

FTIR (neat) ν_{max} : 2941, 2860, 2097, 1457, 1129, 1074, 1053, 958, 912 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{13}\text{H}_{25}\text{N}_3\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 278.1839, found: 278.1849

Deprotection of 100. Synthesis of (Z)-11-azidoundec-6-enal (101).

To a solution of **100** (500 mg, 1.96 mmol) in THF/ H_2O (50 mL, 1:1) was added pyridinium *p*-toluenesulfonic acid (984 mg, 3.92 mmol) at room temperature and the solution was warmed to 50°C for 4 hours. After being cooled to room temperature, the reaction was then diluted with water (10 mL) and with Et_2O (15 mL). The aqueous phase was extracted with Et_2O (3 X 30 mL). The combined organic layers were washed with sat. aq. NH_4Cl solution, brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) provided compound **101** as a colorless oil (291 mg, 71%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 9.76 (s, 1H, CHO), 5.35 (m, 2H, H-7 and H-6), 3.26 (t, 2H, $J_{11,10} = 6.9$ Hz, 2H-11), 2.43 (t, 2H, $J_{2,3} = 7.3$, 2H-2), 2.05 (m, 4H, 2H-8 and 2H-5), 1.61 (m, 4H, 2H-3 and 2H-10), 1.41 (m, 4H, 2H-9 and 2H-4).

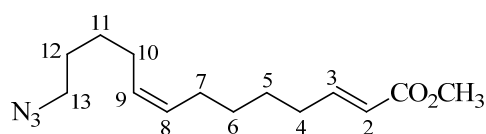
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 202.7 (CHO), 129.9 (C-6), 129.7 (C-7), 51.5 (C-11), 43.9 (C-2), 29.3 (C-10), 28.5 (C-9), 27.1 (C-8), 26.8 (2C, C-5 and C-4), 21.8 (C-3).

FTIR (neat) ν_{\max} : 3007, 2935, 2860, 2720, 2097, 1725, 1458, 1271, 1127, 1074, 961, 891 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{11}\text{H}_{20}\text{NO}$ $[\text{M}+\text{H}-\text{N}_2]^+$: 182.1545, found: 182.1534

Synthesis of (2*E*,8*Z*)-methyl 13-azidotrideca-2,8-dienoate (**102**).

To a solution of **101** (200 mg, 0.96 mmol) in CH_2Cl_2 (30 mL) was added (methoxycarbonylmethylene)triphenylphosphorane (642 mg, 1.92 mmol) at room temperature and the mixture was stirred overnight. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 95:5 hexanes/EtOAc) to provide compound **102** as a colorless oil (219 mg, 86%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 6.96 (dt, 1H, $J_{3,2} = 15.6$, $J_{3,4} = 7.0$ Hz, H-3), 5.81 (dt, 1H, $J_{2,3} = 15.6$, $J_{2,4} = 1.5$ Hz, H-2), 5.35 (m, 2H, H-8 and H-9), 3.71 (s, 3H, COCH_3), 3.26 (t, 2H, $J_{13,12} = 6.9$ Hz, 2H-13),

2.21 (m, 2H, 2H-4), 2.05 (m, 4H, 2H-10 and 2H-7), 1.60 (m, 2H, 2H-12), 1.51-1.33 (m, 6H, 2H-11, 2H-5 and 2H-6).

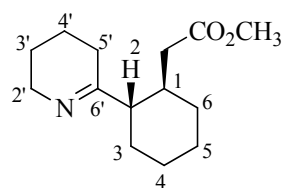
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 167.3 (COCH_3), 149.6 (C-3), 130.2 (C-8), 129.4 (C-9), 121.1 (C-2), 51.5 (COCH_3 and C-13), 32.2 (C-4), 29.2 (C-6), 28.6 (C-12), 27.7 (C-5), 27.1 (C-11), 26.8 (C-10 and C-7).

FTIR (neat) ν_{\max} : 2934, 2859, 2097, 1726, 1658, 1436, 1272, 1200, 1176, 1041, 981, 849 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{14}\text{H}_{23}\text{N}_3\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 288.1682, found: 288.1683

Cyclization of **102**. Synthesis of *rac*-methyl 2-[(1*R*,2*S*)-2-(3,4,5,6-tetrahydropyridin-2-yl)cyclohexyl]acetate (**103**).

A solution of compound **102** (80 mg, 0.30 mmol) in a mixture of DMF/EtOH (10 mL, 4:1) was heated in a microwave reactor at 140°C for 3 hour. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The resulting reaction crude was then purified by column chromatography (silica gel, gradient from CH_2Cl_2 to 97:3 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford compound **103** (53 mg, 74%) as a pale yellow oil.



$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 3.63 (s, 3H, COCH_3), 3.53 (m, 2H, 2H-2'), 2.31 (m, 1H, $\text{CH}_2\text{CO}_2\text{CH}_3$), 2.17-1.96 (m, 4H, 2H-5', $\text{CH}_2\text{CO}_2\text{CH}_3$ and H-1), 1.88 (m, 1H, H-2), 1.81 (m, 1H, H-6 α), 1.76-1.67 (m, 3H, 2H-4 and H-3 α), 1.66-1.58 (m, 2H, 2H-4'), 1.53 (m, 2H,

2H-3'), 1.36-1.19 (m, 3H, 2H-5 and H-3 β), 1.02 (m, 1H, H-6 β).

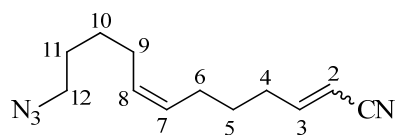
^{13}C -NMR (100 MHz, CDCl_3): δ 173.6 (CO_2CH_3), 173.5 ($\text{C}=\text{N}$), 54.8 (C-2), 51.4 (CO_2CH_3), 49.2 (C-2'), 39.5 ($\text{CH}_2\text{CO}_2\text{CH}_3$), 36.5 (C-1), 32.5 (C-6), 31.0 (C-3), 27.1 (C-5'), 26.1 (C-4), 26.0 (C-5), 22.1 (C-3'), 19.6 (C-4').

FTIR (neat) ν_{max} : 2951, 2869, 1738, 1637, 1437, 1371, 1294, 1163, 1018, 987 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{14}\text{H}_{24}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 238.1802, found: 238.1810

Synthesis of (7Z)-12-azidododeca-2,7-dienenitrile (**104**).

A suspension of NaH (92 mg of 60% in mineral oil, 2.31 mmol) in dry THF (25 mL) was cooled to 0°C. Diethyl (cyanomethyl)phosphonate (0.36 mL, 2.31 mmol) was added dropwise and the reaction mixture was warmed to room temperature over 1 hour. Then a solution of **97** (300 mg, 1.54 mmol) in dry THF (15 mL) was added dropwise at room temperature and the mixture was stirred for 5 hours. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) yielded compound **104** as a colorless oil (323 mg, 96%).



^1H -NMR (300 MHz, CDCl_3 , 4:6 mixture of *E/Z* isomers):

δ 6.71 (dt, 0.4H, $J_{3,2} = 16.3$, $J_{3,4} = 6.9$ Hz, H-3, *E* isomer), 6.48 (dt, 0.6H, $J_{3,2} = 10.8$, $J_{3,4} = 7.7$ Hz, H-3, *Z* isomer), 5.35 (m, 3H, H-2, H-7 and H-8), 3.27 (t, 2H, $J_{12,11} = 6.8$ Hz, 2H-12), 2.44 (m, 1.2H, H-4, *Z* isomer), 2.23 (m, 0.8H, H-4, *E* isomer), 2.06 (m, 4H, 2H-6 and 2H-9), 1.64-1.39 (m, 6H, 2H-11, 2H-5 and 2H-10).

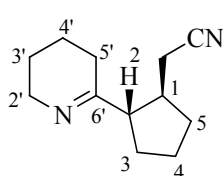
^{13}C -NMR (75 MHz, CDCl_3 , 4:6 mixture of *E/Z* isomers): δ 155.9 (C-3, *E* isomer), 155.0 (C-3, *Z* isomer), 130.3 (C-7), 129.2 (C-8), 117.6 (CN, *Z* isomer), 116.1 (CN, *E* isomer), 100.0 (C-2, *E* isomer), 99.9 (C-2, *Z* isomer), 51.5 (C-12), 32.9 (C-4, *E* isomer), 31.6 (C-4, *Z* isomer), 28.5 (C-11), 28.3 (C-5), 26.8 (C-6 and C-10), 26.5 (C-9).

FTIR (neat) ν_{max} : 2936, 2862, 2222, 2097, 1634, 1456, 1270, 968, 739 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{12}\text{H}_{22}\text{N}_5$ $[\text{M}+\text{NH}_4]^+$: 236.1870, found: 236.1874

Cyclization of **104**. Synthesis of *rac*-2-[(1*R*,2*S*)-2-(3,4,5,6-tetrahydropyridin-2-yl)cyclopentyl]acetonitrile (**105**).

A solution of compound **104** (75 mg, 0.34 mmol) in a mixture of DMF/EtOH (12 mL, 4:1) was heated in a microwave reactor at 140°C for 2 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The resulting reaction crude was then purified by column chromatography (silica gel, gradient from CH₂Cl₂ to 97:3 CH₂Cl₂/MeOH) to afford compound **105** (23 mg, 35%) as a pale yellow oil.



¹H-NMR (400 MHz, CDCl₃): δ 3.55 (m, 2H, 2H-2'), 2.46 (m, 3H, CH₂CN, H-1), 2.27 (m, 1H, H-2), 2.17 (m, 1H, H-5'α), 2.10-1.96 (m, 3H, H-3α, H-5α and H-5'β), 1.70 (m, 4H, 2H-4 and 2H-4'), 1.57 (m, 3H, 2H-3' and H-3β), 1.48 (m, 1H, H-5β).

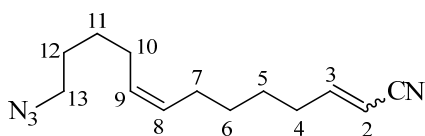
¹³C-NMR (100 MHz, CDCl₃): δ 171.0 (C=N), 119.4 (CN), 54.6 (C-2), 49.3 (C-2'), 38.1 (C-1), 31.5 (C-5), 31.2 (C-3), 28.9 (C-5'), 23.6 (C-4), 22.2 (C-3'), 21.6 (CH₂CN), 19.5 (C-4').

FTIR (neat) v_{max}: 2956, 2246, 1688, 1655, 1555, 1450, 1422, 1379, 1187, 1073, 974, 917 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₂H₁₉N₂ [M+H]⁺: 191.1543, found: 191.1549

Synthesis of (8*Z*)-13-azidotrideca-2,8-dienenitrile (**106**).

A suspension of NaH (71 mg of 60% in mineral oil, 1.78 mmol) in dry THF (20 mL) was cooled to 0°C. Diethyl (cyanomethyl)phosphonate (0.28 mL, 1.78 mmol) was added dropwise and the reaction mixture was warmed to room temperature over 1 hour. Then a solution of **101** (250 mg, 1.19 mmol) in dry THF (15 mL) was added dropwise at room temperature and the mixture was stirred for 4 hours. The reaction was quenched with saturated NH₄Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) yielded compound **106** as a colorless oil (241 mg, 87%).



¹H-NMR (300 MHz, CDCl₃, mixture 1:1 of *E/Z* isomers): δ 6.70 (dt, 0.5H, *J*_{3,2} = 16.4, *J*_{3,4} = 7.0 Hz, H-3, *E* isomer), 6.46 (dt, 0.5H, *J*_{3,2} = 11.0, *J*_{3,4} = 7.7 Hz, H-3, *Z* isomer), 5.34 (m, 3H, H-2, H-8 and H-9), 3.25 (t, 2H, *J*_{13,12} = 6.9 Hz, 2H-13), 2.41 (m, 1H, H-4, *Z* isomer), 2.21 (m, 1H, H-4, *E* isomer), 2.04 (m, 4H, 2H-7 and 2H-10), 1.58 (m, 2H, 2H-12), 1.51-1.32 (m, 6H, 2H-11, 2H-5 and 2H-6).

¹³C-NMR (75 MHz, CDCl₃, mixture 1:1 of *E/Z* isomers): δ 156.0 (C-3, *E* isomer), 155.1 (C-3, *Z* isomer), 129.9 (C-8), 129.6 (C-9), 117.7 (CN, *Z* isomer), 116.2 (CN, *E* isomer), 99.0 (C-2,

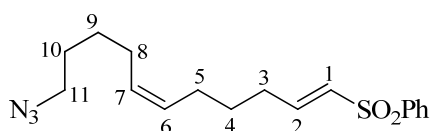
E isomer), 99.7 (C-2, *Z* isomer), 51.5 (C-13), 33.3 (C-4, *E* isomer), 31.9 (C-4, *Z* isomer), 29.1 (C-6), 28.5 (C-12), 27.9 (C-11), 27.3 (C-5), 26.8 (2C, C-7 and C-10).

FTIR (neat) ν_{\max} : 2935, 2860, 2221, 2097, 1622, 1456, 1249, 739 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{13}\text{H}_{20}\text{N}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 255.1580, found: 255.1578

Synthesis of {[*(1E,6Z)*-11-azidoundeca-1,6-dien-1-yl]sulfonyl}benzene (**107**).

To a solution of methyl phenyl sulfone (182 mg, 1.16 mmol) in THF (25 mL), cooled at -78°C , *n*-BuLi (0.80 mL, 1.6 M in hexane, 1.28 mmol) was added. The solution was stirred for 30 min and a solution of **97** (250 mg, 1.28 mmol) in THF (10 mL) was added at -78°C . The resulting solution was stirred for 30 minutes and then warmed to room temperature over 2 hours. The reaction mixture was quenched with a saturated solution of NH_4Cl (15 mL) and extracted with EtOAc (3 X 30 mL). The organic layer was dried with MgSO_4 , filtered and concentrated in vacuo. The crude alcohol was dissolved in CH_2Cl_2 (15 mL) at 0°C . Et_3N (1.5 mL, 11.6 mmol) and methanesulfonyl chloride (0.13 mL, 1.74 mmol) were added. After the mixture was stirred for 2 hours at room temperature a saturated solution of NH_4Cl (15 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 X 30 mL) and the combined organic layers were dried with MgSO_4 , filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, gradient from hexanes to 80:20 hexanes/EtOAc) yielded compound **107** as a colorless oil (232 mg, 60%, 2 steps).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.87 (m, 2H, Ar-H), 7.60 (m, 1H, Ar-H), 7.53 (m, 2H, Ar-H), 6.99 (dt, 1H, $J_{2,1} = 15.1$, $J_{2,3} = 6.8$ Hz, H-2), 6.31 (dt, 1H, $J_{1,2} = 15.2$, $J_{1,3} = 1.6$ Hz, H-1), 5.34 (m, 2H, H-6 and H-7), 3.25 (t, 2H, $J_{11,10} = 6.8$ Hz, 2H-11), 2.25 (m, 2H, 2H-3), 2.02 (m, 4H, 2H-5 and 2H-8), 1.57 (m, 4H, 2H-4 and 2H-10), 1.41 (m, 2H, 2H-9).

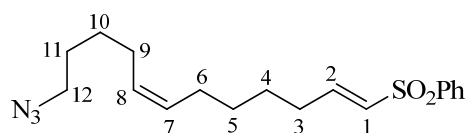
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 147.0 (C-2), 140.9 (Ar-C), 133.4 (Ar-C), 130.7 (C-1), 130.3 (C-6), 129.4 (2C, Ar-C), 129.2 (C-7), 127.7 (2C, Ar-C), 51.5 (C-11), 31.1 (C-3), 28.5 (C-10), 27.6 (C-4), 26.8 (2C, C-9 and C-5), 26.6 (C-8).

FTIR (neat) ν_{\max} : 3061, 3006, 2935, 2861, 2096, 1627, 1447, 1319, 1307, 1147, 1087, 817, 753 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{17}\text{H}_{24}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 334.1584, found: 334.1598

Synthesis of {[*(1E,7Z)*-12-azidododeca-1,7-dien-1-yl]sulfonyl}benzene (108**).**

To a solution of methyl phenyl sulfone (136 mg, 0.87 mmol) in THF (20 mL), cooled at -78°C , *n*-BuLi (0.60 mL, 1.6 M in hexane, 0.96 mmol) was added. The solution was stirred for 30 min and a solution of **101** (200 mg, 0.96 mmol) in THF (10 mL) was added at -78°C . The resulting solution was stirred for 1 hour at -78°C and then 2 hours at room temperature. The reaction mixture was quenched with a saturated solution of NH_4Cl (15 mL) and extracted with EtOAc (3 X 30 mL). The organic layer was dried with MgSO_4 , filtered and concentrated in vacuo. The crude alcohol was dissolved in CH_2Cl_2 (15 mL) at 0°C . Et_3N (1.2 mL, 8.7 mmol) and methanesulfonyl chloride (0.1 mL, 1.31 mmol) were added. After the mixture was stirred for 2 hours at room temperature a saturated solution of NH_4Cl (15 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 X 30 mL) and the combined organic layers were dried with MgSO_4 , filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, gradient from hexanes to 80:20 hexanes/EtOAc) yielded compound **108** as a colorless oil (190 mg, 63%, 2 steps).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.88 (m, 2H, Ar-H), 7.61 (m, 1H, Ar-H), 7.54 (m, 2H, Ar-H), 6.99 (dt, 1H, $J_{2,1} = 15.2$, $J_{2,3} = 6.8$ Hz, H-2), 6.31 (dt, 1H, $J_{1,2} = 15.2$, $J_{1,3} = 1.4$ Hz, H-1), 5.34 (m, 2H, H-7 and H-8), 3.27 (t, 2H, $J_{12,11} = 6.8$ Hz, 2H-12), 2.25 (m, 2H, 2H-3), 2.03 (m, 4H, 2H-6 and 2H-9), 1.58 (m, 2H, 2H-11), 1.51-1.33 (m, 6H, 2H-10, 2H-5 and 2H-4).

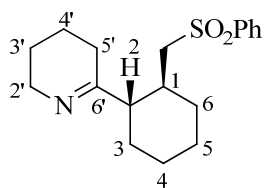
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 147.1 (C-2), 140.9 (Ar-C), 133.4 (Ar-C), 130.6 (C-1), 129.9 (C-8), 129.7 (C-7), 129.4 (2C, Ar-C), 127.7 (2C, Ar-C), 51.5 (C-12), 31.5 (C-3), 29.2 (C-5), 28.6 (C-11), 27.3 (C-4), 27.0 (C-10), 26.8 (2C, C-9 and C-6).

FTIR (neat) ν_{max} : 3005, 2932, 2858, 2096, 1626, 1447, 1319, 1307, 1291, 1147, 1986, 753, 688 cm^{-1} .

HRMS-ESI (*m/z*): calcd for $\text{C}_{18}\text{H}_{25}\text{N}_3\text{NaO}_2\text{S}$ [$\text{M}+\text{Na}$] $^{+}$: 370.1560, found: 370.1572

Cyclization of **108. Synthesis of *rac*-6-[(1*S*,2*S*)-2-[(phenylsulfonyl)methyl]cyclohexyl]-2,3,4,5-tetrahydropyridine (**109**).**

A solution of compound **108** (70 mg, 0.20 mmol) in a mixture of DMF/EtOH (8 mL, 4:1) was heated in a microwave reactor at 140°C for 2 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The resulting reaction crude was then purified by column chromatography (silica gel, gradient from CH_2Cl_2 to 97:3 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford compound **109** (32 mg, 50%) as a pale yellow oil.



$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.87 (m, 2H, Ar-H), 7.64 (m, 1H, Ar-H), 7.56 (m, 2H, Ar-H), 3.45 (m, 2H, 2H-2'), 3.17 (dd, 1H, $J = 14.4$, $J = 1.8$ Hz, $\text{CH}_2\text{SO}_2\text{Ph}$), 2.86 (dd, 1H, $J = 14.4$, $J = 9.1$, $\text{CH}_2\text{SO}_2\text{Ph}$), 2.26 (m, 1H, H-6 α), 2.11 (m, 1H, H-1), 1.97 (m, 2H, 2H-5'), 1.93 (m, 1H, H-2), 1.77-1.68 (m, 3H, 2H-4, H-3 α), 1.62-1.48 (m, 4H, 2H-3' and 2H-4'), 1.32 (m, 1H, H-3 β), 1.25 (m, 2H, 2H-5), 1.13 (m, 1H, H-6 β).

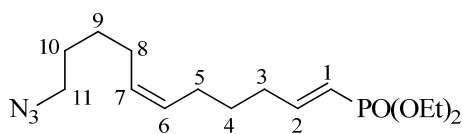
$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 173.0 (C=N), 140.3 (Ar-C), 133.6 (Ar-C), 129.4 (2C, Ar-C), 127.9 (2C, Ar-C), 60.2 ($\text{CH}_2\text{SO}_2\text{Ph}$), 54.3 (C-2), 49.2 (C-2'), 34.5 (C-1), 33.1 (C-6), 30.8 (C-3), 26.5 (C-5'), 25.9 (C-5), 25.7 (C-4), 22.2 (C-3'), 19.5 (C-4').

FTIR (neat) ν_{max} : 2929, 2855, 1699, 1660, 1652, 1447, 1304, 1145, 1086, 814, 748, 690 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{18}\text{H}_{26}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 320.1679, found: 320.1688

Synthesis of diethyl [(1*E*,6*Z*)-11-azidoundeca-1,6-dien-1-yl]phosphonate (**110**):

Tetraethylmethylene diphosphonate (291 mg, 1.01 mmol) in dry THF (5 mL) was added to a suspension of NaH (41 mg, 1.01 mmol) in dry THF (15 mL) at 0°C. After 30 minutes a solution of aldehyde **97** (130 mg, 0.67 mmol) in THF (8 mL) was added dropwise and the reaction mixture was stirred at 0°C for 45 minutes. The reaction was warmed to room temperature and then quenched with saturated NH_4Cl . The mixture was extracted with EtOAc (3 X 30 mL) and the organic layer was dried with MgSO_4 , filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography (silica gel, gradient from hexanes to 50:50 hexanes/EtOAc) to obtain compound **110** as a colorless oil (205 mg, 93%).



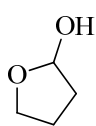
$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 6.77 (ddt, 1H, $J_{2,\text{P}} = 23.4$, $J_{2,1} = 17.1$, $J_{2,3} = 6.5$ Hz, H-2), 5.64 (ddt, 1H, $J_{1,\text{P}} = 20.9$, $J_{1,2} = 17.1$, $J_{1,3} = 1.5$ Hz, H-1), 5.36 (m, 2H, H-6 and H-7), 4.06 (m, 4H, OCH_2CH_3), 3.26 (t, 2H, $J_{11,10} = 6.9$ Hz, 2H-11), 2.23 (m, 2H, 2H-3), 2.07 (m, 4H, 2H-8 and 2H-5), 1.66-1.37 (m, 6H, 2H-4, 2H-9 and 2H-10), 1.31 (t, 6H, $J = 7.1$ Hz, OCH_2CH_3).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 153.6 (d, $J_{\text{C,P}} = 4$ Hz, C-2), 130.0 (C-6), 129.6 (C-7), 117.2 (d, $J_{\text{C,P}} = 188$ Hz, C-1), 61.7 (2C, d, $J_{\text{C,P}} = 6$ Hz, OCH_2CH_3), 51.5 (C-11), 33.8 (d, $J_{\text{C,P}} = 22$ Hz, C-3), 28.6 (C-10), 27.9 (C-4), 26.9 (2C, C-5 and C-9), 26.7 (C-8), 16.5 (2C, d, $J_{\text{C,P}} = 7$ Hz, OCH_2CH_3).

FTIR (neat) ν_{max} : 3467, 2981, 2933, 2862, 2097, 1633, 1456, 1445, 1248, 1055, 1028, 963, 832 cm^{-1} .

HRMS-ESI (m/z): calcd for $C_{15}H_{29}N_3O_3P$ $[M+H]^+$: 330.1941, found: 330.1947

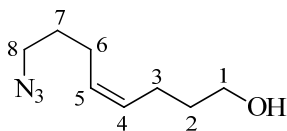
2.3.3.3.- Synthesis of pirrolines with 3,3a,4,5,6,7-hexahydro-2H-indol core.



Synthesis of tetrahydrofuran-2-ol (111): Diisobutylaluminium hydride (38.8 mL, 1.0 M solution in hexanes, 38.8 mmol) was added dropwise to a solution of γ -butyrolactone (2.3 mL, 29.9 mmol) in CH_2Cl_2 (35 mL) at $-78^\circ C$. The resulting solution was stirred at $-78^\circ C$ for one hour and then quenched with EtOAc. The reaction was warmed to room temperature and then poured into a solution of sat. aq. Na-K tartrate (100 mL). The resulting mixture was vigorously stirred until both the aqueous and the organic layers were clear (1 hour and 30 minutes). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 X 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude lactol **111** (2.2 g, 85%) was used without further purification.

Wittig reaction. Synthesis of (Z)-8-azidoct-4-en-1-ol (112).

Phosphonium salt **4** (7.52 g, 17.1 mmol) was dissolved in dry CH_2Cl_2 (8 mL). THF (72 mL) was added and the solution was cooled to $-78^\circ C$. Then KHMDS (34.2 mL, 17.1 mmol, 0.5 M solution in toluene) was added. After the reaction mixture was stirred for 30 minutes at $-78^\circ C$, a solution of aldehyde **111** (1000 mg, 11.4 mmol) in dry THF (30 mL) was added dropwise over 25 minutes. After 1 hour, the reaction mixture was warmed to room temperature over 2 hours and was stirred for an additional 3 hours. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc (3 X 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 3:2 hexanes/EtOAc) provided compound **112** as a colorless oil (1293 mg, 67%).



1H -NMR (300 MHz, $CDCl_3$): δ 5.40 (m, 2H, H-4 and H-5), 3.64 (m, 2H, H-1), 3.27 (t, 2H, $J_{8,7} = 6.8$ Hz, 2H-8), 2.13 (m, 4H, 2H-3 and 2H-6), 1.64 (m, 4H, 2H-2 and 2H-7).

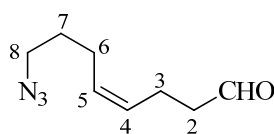
^{13}C -NMR (75 MHz, $CDCl_3$): δ 130.6 (C-4), 128.8 (C-5), 62.5 (C-1), 50.9 (C-8), 32.6 (C-2), 28.8 (C-7), 24.3 (C-6), 23.7 (C-3).

FTIR (neat) ν_{max} : 3351, 3008, 2937, 2868, 2097, 1655, 1452, 1405, 1347, 1287, 1254, 1061, 913, 733 cm^{-1} .

HRMS-ESI (m/z): calcd for $C_8H_{16}NO$ $[M+H-N_2]^+$: 142.1232, found: 142.1212

Oxidation of alcohol **112. Synthesis of (Z)-8-azido-oct-4-enal (**113**).**

PCC (3 g, 14.2 mmol) was added to a solution of **113** (1.2 g, 7.09 mmol) in CH₂Cl₂ (30 mL) at room temperature. The mixture was stirred for 2 hours and then it was filtered through a plug of Celite. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) provided compound **113** as a colorless oil (948 mg, 80%).



¹H-NMR (300 MHz, CDCl₃): δ 9.77 (s, 1H, CHO), 5.39 (m, 2H, H-4 and H-5), 3.28 (t, 2H, *J*_{8,7} = 6.8 Hz, 2H-8), 2.50 (m, 2H, 2H-2), 2.37 (m, 2H, 2H-3), 2.15 (m, 2H, 2H-6), 1.65 (m, 2H, 2H-7).

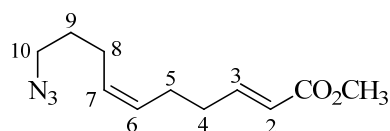
¹³C-NMR (75 MHz, CDCl₃): δ 202.0 (CHO), 129.7 (C-4), 128.8 (C-5), 50.9 (C-8), 43.8 (C-2), 28.7 (C-7), 24.4 (C-6), 20.1 (C-3).

FTIR (neat) *v*_{max}: 3012, 2939, 2868, 2827, 2725, 2098, 1725, 1452, 1409, 1390, 1348, 1288, 1255, 1058, 913, 734 cm⁻¹.

HRMS-ESI (m/z): calcd for C₈H₁₄NO [M+H-N₂]⁺: 140.1075, found: 140.1048

Synthesis of (2E,6Z)-methyl 10-azidodeca-2,6-dienoate (114**).**

To a solution of **113** (250 mg, 1.50 mmol) in CH₂Cl₂ (30 mL) was added (methoxycarbonylmethylene)triphenylphosphorane (1003 mg, 3.0 mmol) at room temperature and the mixture was stirred overnight. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 95:5 hexanes/EtOAc) to provide compound **114** as a colorless oil (275 mg, 82%).



¹H-NMR (300 MHz, CDCl₃): δ 6.95 (dt, 1H, *J*_{3,2} = 15.6, *J*_{3,4} = 6.7 Hz, H-3), 5.84 (d, 1H, *J*_{2,3} = 15.6 Hz, H-2), 5.39 (m, 2H, H-7 and H-6), 3.72 (s, 3H, CO₂CH₃), 3.27 (t, 2H, *J*_{10,9} = 6.8 Hz, 2H-10), 2.24 (m, 4H, 2H-4 and 2H-5), 2.12 (m, 2H, 2H-8), 1.65 (m, 2H, 2H-9).

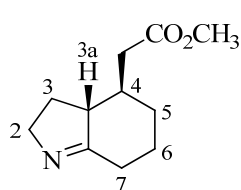
¹³C-NMR (75 MHz, CDCl₃): δ 167.1 (CO₂CH₃), 148.7 (C-3), 129.4 (2C, C-6 and C-7), 121.5 (C-2), 51.6 (CO₂CH₃), 50.9 (C-10), 32.3 (C-4), 28.7 (C-9), 25.9 (C-5), 24.4 (C-8).

FTIR (neat) *v*_{max}: 3010, 2950, 2867, 2098, 1726, 1660, 1436, 1344, 1271, 1206, 1177, 1155, 1042, 977, 854 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₁H₁₈N₃O₂ [M+H]⁺: 224.1394, found: 224.1389

Cyclization of **114**. Synthesis of *rac*-methyl 2-[(3a*R*,4*R*)-3,3a,4,5,6,7-hexahydro-2*H*-indol-4-yl]acetate (**115**).

A solution of compound **114** (60 mg, 0.27 mmol) in dry MeOH (10 mL) was heated in a microwave reactor at 140°C for 2 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude reaction was then purified by column chromatography (silica gel, gradient from CH₂Cl₂ to 97:3 CH₂Cl₂/MeOH) to afford compound **115** (36 mg, 68%) as a yellow oil.



¹H-NMR (400 MHz, CDCl₃): δ 3.87 (m, 1H, H-2α), 3.66 (s, 3H, CO₂CH₃), 3.58 (m, 1H, H-2β), 2.66 (m, 1H, H-7α), 2.42 (dd, 1H, *J* = 14.8, *J* = 4.6 Hz, CH₂CO₂CH₃), 2.32 (m, 1H, H-3a), 2.21 (dd, 1H, *J* = 14.8, *J* = 8.8 Hz, CH₂CO₂CH₃), 2.15-2.08 (m, 2H, H-3α and H-7β), 1.95 (m, 1H, H-6α), 1.87 (m, 1H, H-5α), 1.68 (m, 1H, H-4), 1.49-1.40 (m, 2H, H-3β and H-6β), 1.25 (m, 1H, H-5β).

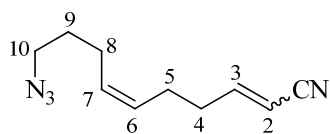
¹³C-NMR (100 MHz, CDCl₃): δ 178.3 (C=N), 173.1 (CO₂CH₃), 59.1 (C-2), 53.3 (C-3a), 51.7 (CO₂CH₃), 42.7 (C-4), 40.4 (CH₂CO₂CH₃), 31.4 (2C, C-5 and C-7), 28.4 (C-3), 25.2 (C-6).

FTIR (neat) ν_{max}: 2949, 2866, 1737, 1652, 1568, 1436, 1234, 1195, 1155, 1099, 982 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₁H₁₈NO₂ [M+H]⁺: 196.1293, found: 196.1351

Synthesis of (6*Z*)-10-azidodeca-2,6-dienitrile (**116**).

A suspension of NaH (90 mg of 60% in mineral oil, 2.25 mmol) in dry THF (20 mL) was cooled to 0°C. Diethyl(cyanomethyl)phosphonate (0.35 mL, 2.25 mmol) was added dropwise and the reaction mixture was warmed to room temperature over 1 hour. Then a solution of **113** (250 mg, 1.50 mmol) in dry THF (12 mL) was added dropwise at room temperature and the mixture was stirred for 4 hours. The reaction was quenched with saturated NH₄Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) yielded compound **116** as a colorless oil (254 mg, 89%).



¹H-NMR (300 MHz, CDCl₃ 4:6 mixture of *E/Z* isomers): δ 6.70 (dt, 0.4H, *J*_{3,2} = 16.3, *J*_{3,4} = 6.6 Hz, H-3, *E* isomer), 6.47 (dt, 0.6H, *J*_{3,2} = 10.8, *J*_{3,4} = 7.6 Hz, H-3, *Z* isomer), 5.41 (m, 2H, H-7 and H-6), 5.34 (m, 1H, H-2), 3.28 (t, 2H, *J*_{10,9} = 6.7 Hz, 2H-10), 2.49 (m, 1.2H, H-4, *Z* isomer), 2.29 (m, 0.8H, H-4, *E* isomer), 2.24 (m, 2H, 2H-5), 2.12 (m, 2H, 2H-8), 1.65 (m, 2H, 2H-9).

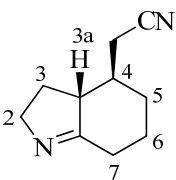
^{13}C -NMR (75 MHz, CDCl_3 , 4:6 mixture of *E/Z* isomers): δ 155.2 (C-3, *E* isomer), 154.2 (C-3, *Z* isomer), 130.0 (C-7), 128.7 (C-6), 117.5 (CN, *E* isomer), 116.1 (CN, *Z* isomer), 100.5 (C-2, *E* isomer), 100.2 (C-2, *Z* isomer), 50.9 (C-10), 33.3 (C-4, *E* isomer), 31.9 (C-4, *Z* isomer), 28.7 (C-9), 26.0 (C-5, *Z* isomer), 25.5 (C-5, *E* isomer), 24.4 (C-8).

FTIR (neat) ν_{max} : 3012, 2939, 2867, 2223, 2098, 1678, 1634, 1451, 1347, 1288, 1255, 967, 745 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{10}\text{H}_{15}\text{N}_4$ $[\text{M}+\text{H}]^+$: 191.1291, found: 191.1293

Cyclization of **116**. Synthesis of *rac*-2-[(3*aR*,4*R*)-3,3*a*,4,5,6,7-hexahydro-2*H*-indol-4-yl]acetonitrile (**117**).

A solution of compound **116** (65 mg, 0.34 mmol) in dry MeOH (12 mL) was heated in a microwave reactor at 140°C for 2 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude reaction was then purified by column chromatography (silica gel, gradient from CH_2Cl_2 to 97:3 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford compound **117** (39 mg, 70%) as a yellow oil.

 **^1H -NMR (400 MHz, CDCl_3):** δ 3.93 (m, 1H, H-2 α), 3.65 (m, 1H, H-2 β), 2.71 (m, 1H, H-7 α), 2.48 (dd, 1H, $J = 16.8$, $J = 4.4$ Hz, CH_2CN), 2.47 (m, 1H, H-3*a*), 2.35 (dd, 1H, $J = 16.8$, $J = 6.7$ Hz, CH_2CN), 2.26 (m, 1H, H-3 α), 2.16 (m, 1H, H-7 β), 2.04 (m, 1H, H-6 α), 1.98 (m, 1H, H-5 α), 1.57 (m, 1H, H-4), 1.48 (m, 3H, H-3 β , H-6 β and H-5 β).

^{13}C -NMR (100 MHz, CDCl_3): δ 177.1 (C=N), 118.2 (CN), 59.3 (C-2), 52.5 (C-3*a*), 42.3 (C-4), 31.0 (C-7), 30.8 (C-5), 28.3 (C-3), 24.8 (C-6), 23.4 (CH_2CN).

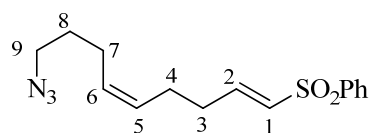
FTIR (neat) ν_{max} : 2935, 2869, 2245, 1655, 1447, 1425, 1296, 1261, 1033, 987 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{10}\text{H}_{15}\text{N}_2$ $[\text{M}+\text{H}]^+$: 163.1230, found: 163.1226

Synthesis of {[(1*E*,5*Z*)-9-azidonona-1,5-dien-1-yl]sulfonyl}benzene (**118**).

To a solution of methyl phenyl sulfone (172 mg, 1.10 mmol) in THF (25 mL), cooled at -78°C , *n*-BuLi (0.75 mL, 1.6 M in hexane, 1.20 mmol) was added. The solution was stirred for 30 minutes and a solution of **113** (200 mg, 1.20 mmol) in THF (10 mL) was added at -78°C . The resulting solution was stirred for 1 hour at -78°C and then 2 hours at room temperature. The reaction mixture was quenched with a saturated solution of NH_4Cl (15 mL) and extracted with EtOAc (3 X 30 mL). The organic layer was dried with MgSO_4 , filtered and concentrated in vacuo. The crude alcohol was dissolved in CH_2Cl_2 (15 mL) at 0°C . Et_3N (1.53 mL, 11 mmol)

and methanesulfonyl chloride (0.12 mL, 1.65 mmol) were added. After the mixture was stirred for 2 hours at room temperature a saturated solution of NH_4Cl (15 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 X 30 mL) and the combined organic layers were dried with MgSO_4 , filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, gradient from hexanes to 80:20 hexanes/EtOAc) yielded compound **118** as a colorless oil (208 mg, 62%, 2 steps).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.86 (m, 2H, Ar-H), 7.59 (m, 1H, Ar-H), 7.52 (m, 2H, Ar-H), 6.95 (dt, 1H, $J_{2,1} = 15.1$, $J_{2,3} = 6.6$ Hz, H-2), 6.33 (dt, 1H, $J_{1,2} = 15.1$, $J_{1,3} = 1.5$ Hz, H-1), 5.35 (m, 2H, H-5 and H-6), 3.25 (t, 2H, $J_{9,8} = 6.7$ Hz, 2H-9), 2.28 (m, 2H, 2H-3), 2.21 (m, 2H, 2H-4), 2.08 (m, 2H, 2H-7), 1.63 (m, 2H, 2H-8).

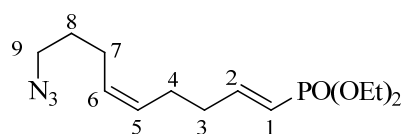
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 146.3 (C-2), 140.8 (Ar-C), 133.4 (Ar-C), 131.0 (C-1), 130.0 (C-6), 129.4 (2C, Ar-C), 128.6 (C-5), 127.7 (2C, Ar-C), 50.9 (C-9), 31.5 (C-3), 28.6 (C-8), 25.4 (C-4), 24.4 (C-7).

FTIR (neat) ν_{max} : 2936, 2097, 1627, 1447, 1318, 1307, 1146, 1087, 827, 752 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{15}\text{H}_{20}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 306.1271, found: 306.1274

Synthesis of diethyl [(1E,5Z)-9-azidonona-1,5-dien-1-yl]phosphonate (**119**).

Tetraethylmethylene diphosphonate (233 mg, 0.81 mmol) in dry THF (5 mL) was added to a suspension of NaH (32 mg, 0.81 mmol) in dry THF (15 mL) at 0°C . After 30 minutes a solution of aldehyde **113** (90 mg, 0.54 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0°C for 45 minutes. The reaction was warmed to room temperature and then quenched with saturated NH_4Cl . The mixture was extracted with EtOAc (3 X 30 mL) and the organic layer was dried with MgSO_4 , filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography (silica gel, gradient from hexanes to 40:60 hexanes/EtOAc) to obtain compound **119** as a colorless oil (135 mg, 83%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 6.75 (ddt, 1H, $J_{2,P} = 21.9$, $J_{2,1} = 17.1$, $J_{2,3} = 6.2$ Hz, H-2), 5.66 (ddt, 1H, $J_{1,P} = 20.3$, $J_{1,2} = 17.1$, $J_{1,3} = 1.5$ Hz, H-1), 5.38 (m, 2H, H-5 and H-6), 4.06 (m, 4H, OCH_2CH_3), 3.26 (t, 2H, $J_{9,8} = 6.8$ Hz, 2H-9), 2.25 (m, 2H, 2H-3), 2.11 (m, 4H, 2H-4 and 2H-7), 1.65 (m, 2H, 2H-8), 1.31 (t, 6H, $J = 7.1$ Hz, OCH_2CH_3).

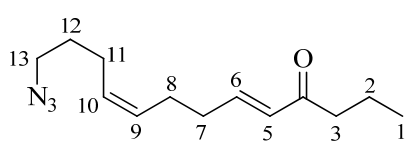
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 152.8 (d, $J_{C,P} = 4$ Hz, C-2), 129.4 (2C, C-5 and C-6), 117.5 (d, $J_{C,P} = 188$ Hz, C-1), 61.7 (2C, d, $J_{C,P} = 6$ Hz, OCH_2CH_3), 50.9 (C-9), 34.1 (d, $J_{C,P} = 22$ Hz, C-3), 28.7 (C-8), 25.4 (C-4), 24.4 (C-7), 16.5 (2C, d, $J_{C,P} = 6$ Hz, OCH_2CH_3).

FTIR (neat) ν_{\max} : 3468, 2982, 2934, 2869, 2097, 1633, 1445, 1392, 1247, 1055, 1028, 964, 842 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{13}\text{H}_{25}\text{N}_3\text{O}_3\text{P}$ $[\text{M}+\text{H}]^+$: 302.1628, found: 302.1639

Synthesis of (5*E*,9*Z*)-13-azidotrideca-5,9-dien-4-one (**120**).

A suspension of NaH (96 mg of 60% in mineral oil, 2.40 mmol) in dry THF (20 mL) was cooled to -78°C . Dimethyl (2-oxopentyl)phosphonate (compound **90**, 466 mg, 2.40 mmol) dissolved in THF (10 mL) was added dropwise and the reaction mixture was stirred for 20 minutes at -78°C and 20 minutes at 0°C . Then a solution of **113** (200 mg, 1.20 mmol) in dry THF (10 mL) was added dropwise and the mixture was stirred for 30 minutes at 0°C . The reaction was warmed to room temperature and after 1 hour and 30 minutes it was quenched with water and extracted with Et_2O (3 X 30 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/ EtOAc) yielded compound **120** as a colorless oil (231 mg, 82%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 6.80 (dt, 1H, $J_{6,5} = 15.9$, $J_{6,7} = 6.6$ Hz, H-6), 6.10 (dt, 1H, $J_{5,6} = 15.9$, $J_{5,7} = 1.4$ Hz, H-5), 5.39 (m, 2H, H-9 and H-10), 3.27 (t, 2H, $J_{13,12} = 6.8$ Hz, 2H-13), 2.50 (t, 2H, $J_{3,2} = 7.3$ Hz, 2H-3), 2.25 (m, 4H, 2H-7 and 2H-8), 2.12 (m, 2H, 2H-11), 1.65 (m, 4H, 2H-2 and 2H-12), 0.93 (t, 3H, $J_{1,2} = 7.4$ Hz, CH_3).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 200.8 (C=O), 146.2 (C-6), 130.9 (C-5), 129.5 (2C, C-9 and C-10), 50.9 (C-13), 42.2 (C-3), 32.5 (C-7), 28.7 (C-12), 26.0 (C-8), 24.4 (C-11), 17.8 (C-2), 14.0 (C-1).

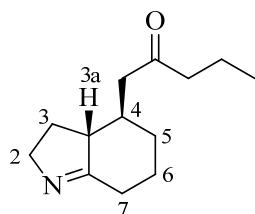
FTIR (neat) ν_{\max} : 3009, 2962, 2935, 2874, 2097, 1676, 1630, 1551, 1458, 1407, 1367, 1288, 1256, 1198, 1132, 977 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{13}\text{H}_{22}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 236.1757, found: 236.1756

Cyclization of **120**. Synthesis of *rac*-1-[(3*aR*,4*R*)-3,3*a*,4,5,6,7-hexahydro-2*H*-indol-4-yl]pentan-2-one (**121**).

A solution of compound **120** (70 mg, 0.30 mmol) in dry MeOH (10 mL) was heated in a microwave reactor at 140°C for 2 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude reaction was then purified by column

chromatography (silica gel, gradient from CH₂Cl₂ to 97:3 CH₂Cl₂/MeOH) to afford compound **121** (41 mg, 66%) as a yellow oil.



¹H-NMR (400 MHz, CDCl₃): δ 3.87 (m, 1H, H-2α), 3.58 (m, 1H, H-2β), 2.66 (m, 1H, H-7α), 2.46 (dd, 1H, *J* = 16.2, *J* = 3.9 Hz, CHCH₂CO), 2.37 (m, 2H, COCH₂CH₂CH₃), 2.32 (dd, 1H, *J* = 16.2, *J* = 8.9 Hz, CHCH₂CO), 2.30 (m, 1H, H-3α), 2.09 (m, 2H, H-3α and H-7β), 1.93 (m, 1H, H-6α), 1.82 (m, 1H, H-5α), 1.74 (m, 1H, H-4), 1.59 (m, 2H, COCH₂CH₂CH₃), 1.47-1.37 (m, 2H, H-3β and H-6β), 1.16 (m, 1H, H-5β), 0.90 (t, 3H, *J* = 7.4 Hz, CH₂CH₂CH₃).

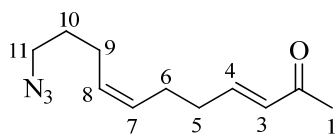
¹³C-NMR (100 MHz, CDCl₃): δ 210.3 (C=O), 178.5 (C=N), 59.0 (C-2), 53.5 (C-3a), 48.7 (CHCH₂CO), 45.7 (CH₂CH₂CH₃), 41.7 (C-4), 31.5 (2C, C-7 and C-5), 28.5 (C-3), 25.3 (C-6), 17.3 (CH₂CH₂CH₃), 13.9 (CH₂CH₂CH₃).

FTIR (neat) v_{max}: 2959, 2935, 2871, 1710, 1653, 1457, 1447, 1410, 1375, 1351, 1295, 1233, 1126, 1021, 984 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₃H₂₂NO [M+H]⁺: 208.1696, found: 208.1698

Synthesis of (3*E*,7*Z*)-11-azidoundeca-3,7-dien-2-one (**122**).

To a solution of **113** (190 mg, 1.13 mmol) in CH₂Cl₂ (20 mL) was added 1-(triphenylphosphoranylidene)-2-propanone (1080 mg, 3.39 mmol) at room temperature and the mixture was stirred for 3 days. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 85:15 hexanes/EtOAc) to provide compound **122** as a colorless oil (190 mg, 81%).



¹H-NMR(300 MHz, CDCl₃): δ 6.78 (dt, 1H, *J*_{4,3} = 15.9, *J*_{4,5} = 6.6 Hz, H-4), 6.08 (dt, 1H, *J*_{3,4} = 15.9, *J*_{3,5} = 1.4 Hz, H-3), 5.39 (m, 2H, H-7 and H-8), 3.27 (t, 2H, *J*_{11,10} = 6.8 Hz, 2H-11), 2.25 (m, 4H, 2H-5 and 2H-6), 2.23 (s, 3H, CH₃), 2.12 (m, 2H, 2H-9), 1.64 (m, 2H, 2H-10).

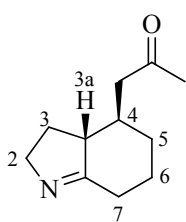
¹³C-NMR(75 MHz, CDCl₃): δ 198.7 (C=O), 147.5 (C-4), 131.8 (C-3), 129.4 (2C, C-7 and C-8), 50.9 (C-11), 32.5 (C-5), 28.7 (C-10), 27.0 (C-10), 25.9 (C-6), 24.4 (C-9).

FTIR (neat) v_{max}: 3345, 3009, 2937, 2866, 2504, 2097, 1712, 1678, 1627, 1553, 1471, 1448, 1363, 1255, 977, 954, 734 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₁H₁₇N₃NaO [M+Na]⁺: 230.1264, found: 230.1255

Cyclization of **122**. Synthesis of *rac*-1-[(3*aR*,4*R*)-3,3*a*,4,5,6,7-hexahydro-2*H*-indol-4-yl]propan-2-one (**123**).

A solution of compound **122** (70 mg, 0.34 mmol) in dry MeOH (12 mL) was heated in a microwave reactor at 140°C for 2 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude reaction was then purified by column chromatography (silica gel, gradient from CH₂Cl₂ to 97:3 CH₂Cl₂/MeOH) to afford compound **123** (39 mg, 64%) as a yellow oil.



¹H-NMR (500 MHz, CDCl₃): δ 3.87 (m, 1H, H-2α), 3.58 (m, 1H, H-2β), 2.66 (m, 1H, H-7α), 2.51 (dd, 1H, *J* = 16.3, *J* = 3.8 Hz, CH₂COCH₃), 2.35 (dd, 1H, *J* = 16.3, *J* = 9.2 Hz, CH₂COCH₃), 2.30 (m, 1H, H-3a), 2.14 (s, 3H, COCH₃), 2.10 (m, 2H, H-3α and H-7β), 1.93 (m, 1H, H-6α), 1.85 (m, 1H, H-5α), 1.73 (m, 1H, H-4), 1.49-1.39 (m, 2H, H-3β and H-6β), 1.16 (m, 1H, H-5β).

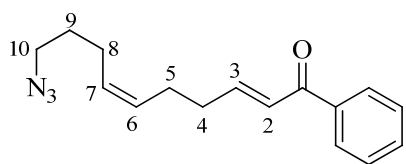
¹³C-NMR (125 MHz, CDCl₃): δ 208.0 (C=O), 178.3 (C=N), 59.0 (C-2), 53.4 (C-3a), 49.6 (CH₂COCH₃), 41.7 (C-4), 31.5 (2C, C-7 and C-5), 30.8 (COCH₃), 28.5 (C-3), 25.3 (C-6).

FTIR (neat) ν_{\max} : 3396, 2937, 2865, 1713, 1652, 1540, 1446, 1429, 1356, 1293, 1265, 1225, 1158, 985 cm⁻¹.

HRMS-ESI (*m/z*): calcd for C₁₁H₁₈NO [M+H]⁺: 180.1383, found: 180.1395

Synthesis of (2*E*,6*Z*)-10-azido-1-phenyldeca-2,6-dien-1-one (**124**).

To a solution of **113** (180 mg, 1.08 mmol) in CH₂Cl₂ (20 mL) was added 1-phenyl-2-(triphenylphosphoranylidene)ethanone (1229 mg, 3.23 mmol) at room temperature and the mixture was stirred for 3 days. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) to provide compound **124** as a colorless oil (227 mg, 78%).



¹H-NMR (300 MHz, CDCl₃): δ 7.93 (m, 2H, Ar-H), 7.55 (m, 1H, Ar-H), 7.47 (m, 2H, Ar-H), 7.05 (dt, 1H, *J*_{3,2} = 15.4, *J*_{3,4} = 6.5 Hz, H-3), 6.89 (dt, 1H, *J*_{2,3} = 15.4, *J*_{2,4} = 1.3 Hz, H-2), 5.43 (m, 2H, H-6 and H-7), 3.28 (t, 2H, *J*_{10,9} = 6.8 Hz, 2H-10), 2.38 (m, 2H, 2H-4), 2.29 (m, 2H, 2H-5), 2.15 (m, 2H, 2H-8), 1.66 (m, 2H, 2H-9).

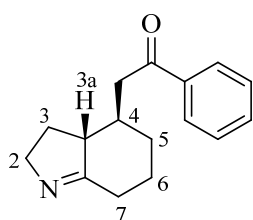
¹³C-NMR (75 MHz, CDCl₃): δ 190.6 (C=O), 148.5 (C-3), 138.2 (Ar-C), 132.5 (Ar-C), 129.4 (2C, C-6 and C-7), 128.5 (4C, Ar-C), 126.6 (C-2), 50.9 (C-10), 32.7 (C-4), 28.7 (C-9), 26.0 (C-5), 24.4 (C-8).

FTIR (neat) ν_{\max} : 3060, 3009, 2935, 2865, 2096, 1670, 1652, 1622, 1598, 1579, 1448, 1348, 1287, 1254, 1231, 1180, 1003, 974, 695 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{16}\text{H}_{20}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 270.1601, found: 270.1606

Cyclization 124. Synthesis of *rac*-2-[(3*aR*,4*R*)-3,3*a*,4,5,6,7-hexahydro-2*H*-indol-4-yl]-1-phenylethanone (125).

A solution of compound **124** (80 mg, 0.30 mmol) in dry MeOH (10 mL) was heated in a microwave reactor at 140°C for 2 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude reaction was then purified by column chromatography (silica gel, gradient from CH_2Cl_2 to 97:3 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford compound **125** (40 mg, 55%) as a yellow oil.



$^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 7.94 (m, 2H, Ar-H), 7.56 (m, 1H, Ar-H), 7.47 (m, 2H, Ar-H), 3.89 (dddd, 1H, $J = 13.0$, $J = 9.5$, $J = 4.3$, $J = 2.0$ Hz, H-2 α), 3.60 (dddd, 1H, $J = 13.0$, $J = 8.6$, $J = 3.9$, $J = 2.1$ Hz, H-2 β), 3.02 (dd, 1H, $J = 16.0$, $J = 3.9$ Hz, CH_2COPh), 2.91 (dd, 1H, $J = 16.0$, $J = 8.8$ Hz, CH_2COPh), 2.69 (m, 1H, H-7 α), 2.43 (m, 1H, H-3 α), 2.19-2.09 (m, 2H, H-3 α and H-7 β), 1.93 (m, 3H, H-4, H-5 α and H-6 α), 1.48 (m, 2H, H-3 β and H-6 β), 1.23 (m, 1H, H-5 β).

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3): δ 199.5 (C=O), 178.4 (C=N), 137.3 (Ar-C), 133.3 (Ar-C), 128.8 (2C, Ar-C), 128.2 (2C, Ar-C), 59.0 (C-2), 53.7 (C-3 α), 44.5 (CH_2COPh), 42.3 (C-4), 31.7 (C-5), 31.5 (C-7), 28.7 (C-3), 25.3 (C-6).

FTIR (neat) ν_{\max} : 3401, 3063, 2944, 2867, 2096, 1682, 1652, 1597, 1580, 1448, 1370, 1347, 1285, 1269, 1231, 1199, 1181, 1001, 753, 692 cm^{-1} .

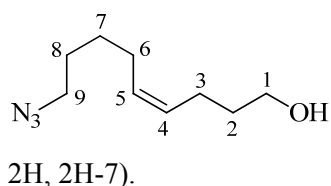
HRMS-ESI (m/z): calcd for $\text{C}_{16}\text{H}_{20}\text{NO}$ $[\text{M}+\text{H}]^+$: 242.1539, found: 242.1541

2.3.3.4.- Synthesis of piperideines with 2,3,4,4*a*,5,6,7,8-octahydroquinoline core.

Wittig reaction. Synthesis of (Z)-9-azidonon-4-en-1-ol (126).

Phosphonium salt **6** (9.26 g, 20.45 mmol) was dissolved in dry CH_2Cl_2 (8 mL). THF (72 mL) was added and the solution was cooled to -78°C. Then KHMDS (40.90 mL, 20.45 mmol, 0.5 M solution in toluene) was added. After the reaction mixture was stirred for 30 minutes at -78°C, a solution of aldehyde **111** (1.2 g, 13.63 mmol) in dry THF (30 mL) was added dropwise

over 25 minutes. After 1 hour, the reaction mixture was warmed to room temperature over 2 hours. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) yielded compound **126** as a colorless oil (1.5 g, 58%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.30 (m, 2H, H-4 and H-5), 3.52 (t, 2H, $J_{1,2} = 6.6$ Hz, 2H-1), 3.18 (t, 2H, $J_{9,8} = 6.8$ Hz, 2H-9), 2.00 (m, 4H, 2H-6 and 2H-3), 1.52 (m, 4H, 2H-2 and 2H-8), 1.36 (m, 2H, 2H-7).

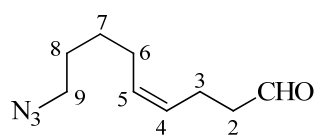
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 129.9 (2C, C-4 and C-5), 62.7 (C-1), 51.5 (C-9), 32.7 (C-2), 28.5 (C-8), 26.8 (2C, C-6 and C-7), 23.7 (C-3).

FTIR (neat) ν_{max} : 3339, 3007, 2936, 2865, 2098, 1654, 1455, 1247, 1060, 913, 732 cm^{-1} .

HRMS-ESI (m/z): $\text{C}_9\text{H}_{18}\text{NO}$ $[\text{M}+\text{H}-\text{N}_2]^+$: 156.1388, found:156.1407

Oxidation of alcohol **126**. Synthesis of (Z)-9-azidonon-4-enal (**127**).

PCC (2.8 g, 13.1 mmol) was added to a solution of **126** (1.2 mg, 6.55 mmol) in CH_2Cl_2 (30 mL) at room temperature. The mixture was stirred for 2 hours and then it was filtered through a plug of Celite. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) provided compound **127** as a colorless oil (937 mg, 79%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 9.71 (s, 1H, CHO), 5.34 (m, 2H, H-4 and H-5), 3.22 (t, 2H, $J_{9,8} = 6.8$ Hz, 2H-9), 2.44 (t, 2H, $J_{2,3} = 7.3$ Hz, 2H-2), 2.31 (m, 2H, 2H-3), 2.04 (m, 2H, 2H-6), 1.55 (m, 2H, 2H-8), 1.39 (m, 2H, 2H-7).

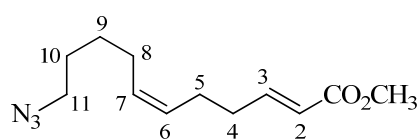
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 201.5 (CHO), 130.6 (C-4), 128.0 (C-5), 51.4 (C-9), 43.7 (C-2), 28.6 (C-8), 26.8 (2C, C-7 and C-6), 20.3 (C-3).

FTIR (neat) ν_{max} : 3011, 2937, 2862, 2724, 2097, 1726, 1456, 1410, 1390, 1351, 1248, 1057, 858, 720 cm^{-1} .

HRMS-ESI (m/z): $\text{C}_9\text{H}_{16}\text{NO}$ $[\text{M}+\text{H}-\text{N}_2]^+$: 154.1232, found:154.1225

Synthesis of (2*E*,6*Z*)-methyl 11-azidoundeca-2,6-dienoate (128).

To a solution of **127** (300 mg, 1.66 mmol) in CH₂Cl₂ (30 mL) was added (methoxycarbonylmethylene)triphenylphosphorane (1110 mg, 3.32 mmol) at room temperature and the mixture was stirred overnight. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 95:5 hexanes/EtOAc) to provide compound **128** as a colorless oil (350 mg, 89%).



¹H-NMR (300 MHz, CDCl₃): δ 6.95 (dt, 1H, *J*_{3,2} = 15.8, *J*_{3,4} = 6.7 Hz, H-3), 5.83 (dt, 1H, *J*_{2,3} = 15.8, *J*_{2,4} = 1.5 Hz, H-2), 5.38 (m, 2H, H-6 and H-7), 3.72 (s, 3H, CO₂CH₃), 3.26 (t, 2H, *J*_{11,10} = 6.8 Hz, 2H-11), 2.23 (m, 4H, 2H-4 and 2H-5), 2.05 (m, 2H, 2H-8), 1.60 (m, 2H, 2H-10), 1.44 (m, 2H, 2H-9).

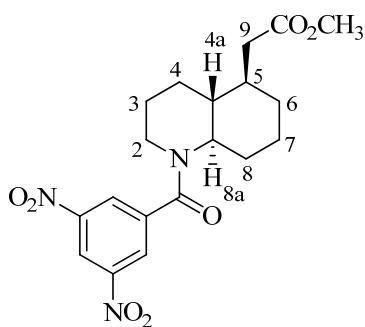
¹³C-NMR (75 MHz, CDCl₃): δ 167.1 (CO₂CH₃), 148.8 (C-3), 130.4 (C-7), 128.6 (C-6), 121.4 (C-2), 51.5 (CO₂CH₃), 51.4 (C-11), 32.3 (C-4), 28.5 (C-10), 26.8 (C-9), 26.7 (C-8), 25.9 (C-5).

FTIR (neat) ν_{max}: 3009, 2945, 2861, 2096, 1725, 1659, 1436, 1341, 1271, 1205, 1173, 1154, 1077, 1042, 978, 853 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₂H₂₀N₃O₂ [M+H]⁺: 238.1550, found: 238.1542

Synthesis of *rac*-methyl 2-[(4*aR*,5*R*,8*aR*)-1-(3,5-dinitrobenzoyl)decahydroquinolin-5-yl]acetate (130).

A solution of compound **128** (85 mg, 0.36 mmol) in dry MeOH (12 mL) was heated in a microwave reactor at 140°C for 3 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude material was dissolved in absolute ethanol (8 mL), cooled to 0°C and sodium borohydride (20 mg, 0.54 mmol) was added. After 45 min the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 X 30 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated in vacuo. The crude oil was dissolved in CH₂Cl₂ (8 mL), cooled to 0°C and Et₃N (0.1 mL, 0.72 mmol) and 3,5-dinitrobenzoyl chloride (124 mg, 0.54 mmol) were added sequentially. After stirring at room temperature for 10 hours the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) to afford compound **130** (80 mg, 55%, 3 steps) as a yellow solid.



$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.99 (t, 1H, $J = 2.2$ Hz, Ar-H), 8.51 (d, 2H, $J = 2.2$ Hz, Ar-H), 3.62 (s, 3H, CO_2CH_3), 3.55 (td, 1H, $J = 11.2$, $J = 3.2$ Hz, H-8a), 3.39 (ddd, 1H, $J_{2\alpha,2\beta} = 13.9$, $J_{2\alpha,3\alpha} = 10.6$, $J_{2\alpha,3\beta} = 5.4$ Hz, H-2 α), 3.25 (ddd, 1H, $J_{2\beta,2\alpha} = 13.9$, $J_{2\beta,3\beta} = 6.5$, $J_{2\beta,3\alpha} = 3.1$ Hz, H-2 β), 2.48 (dd, 1H, $J_{9\alpha,9\beta} = 15.1$, $J_{9\alpha,5} = 4.7$ Hz, H-9 α), 2.17 (m, 1H, H-8 α), 2.10 (dd, 1H, $J_{9\beta,9\alpha} = 15.1$, $J_{9\beta,5} = 8.0$ Hz, H-9 β), 1.91 (m, 1H, H-4 α), 1.83-1.71 (m, 3H, H-3 α , H-6 α and H-7 α), 1.70-1.56 (m, 2H, H-3 β and H-5), 1.55- 1.44 (m, 3H, H-4 α , H-7 β and H-8 β), 1.14 (m, 2H, H-4 β and H-6 β).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 173.2 (CO_2CH_3), 166.2 (C=O amide), 148.4 (2C, Ar-C), 140.6 (Ar-C), 127.3 (2C, Ar-C), 119.3 (Ar-C), 61.4 (C-8a), 51.6 (CO_2CH_3), 42.9 (C-2), 42.1 (C-4a), 39.3 (C-5), 38.2 (C-9), 32.4 (C-6), 29.8 (C-8), 24.5 (C-7), 23.7 (C-3), 23.1 (C-4).

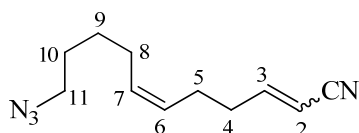
FTIR (KBr) ν_{max} : 3101, 2936, 2865, 1732, 1633, 1538, 1463, 1434, 1345, 1271, 1204, 1168, 1126, 1080, 916, 731 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{19}\text{H}_{24}\text{N}_3\text{O}_7$ $[\text{M}+\text{H}]^+$: 406.1609, found: 406.1607

Mp: 103-105°C

Synthesis of (6Z)-11-azidoundeca-2,6-dienenitrile (**131**).

A suspension of NaH (100 mg of 60% in mineral oil, 2.49 mmol) in dry THF (20 mL) was cooled to 0°C. Diethyl(cyanomethyl)phosphonate (0.39 mL, 2.49 mmol) was added dropwise and the reaction mixture was warmed to room temperature over 1 hour. Then a solution of **127** (300 mg, 1.66 mmol) in dry THF (12 mL) was added dropwise at room temperature and the mixture was stirred for 4 hours. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) yielded compound **131** as a colorless oil (305 mg, 90%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3 4:1 mixture of *E/Z* isomers): δ 6.69 (dt, 0.8H, $J_{3,2} = 16.3$, $J_{3,4} = 6.7$ Hz, H-3, *E* isomer), 6.49 (dt, 0.2H, $J_{3,3} = 10.9$, $J_{3,4} = 7.6$ Hz, H-3, *Z* isomer), 5.48-5.26 (m, 3H, H-2, H-6 and H-7), 3.26 (t, 2H, $J_{11,10} = 6.8$ Hz, 2H-11), 2.48 (m, 0.4H, H-4, *Z* isomer), 2.32-2.13 (m, 3.6H, H-4 *E* isomer and 2H-5), 2.04 (m, 2H, 2H-8), 1.59 (m, 2H, 2H-10), 1.43 (m, 2H, 2H-9).

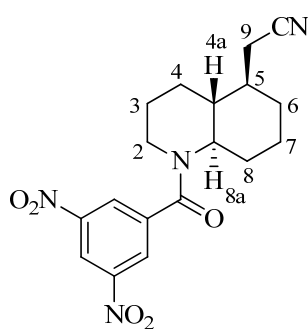
^{13}C -NMR (75 MHz, CDCl_3 4:1 mixture of *E/Z* isomers): δ 155.2 (C-3, *E* isomer), 154.3 (C-3, *Z* isomer), 131.0 (C-7), 127.7 (C-6), 117.5 (CN, *E* isomer), 116.0 (CN, *Z* isomer), 100.3 (C-2, *E* isomer), 100.1 (C-2, *Z* isomer), 51.4 (C-11), 33.3 (C-4, *E* isomer), 31.8 (C-4, *Z* isomer), 28.5 (C-10), 26.8 (C-9), 26.7 (C-8), 25.5 (C-5).

FTIR (neat) ν_{max} : 3011, 2938, 2862, 2223, 2097, 1634, 1455, 1351, 1272, 1248, 966 cm^{-1} .

HRMS-ESI (*m/z*): calcd for $\text{C}_{11}\text{H}_{17}\text{N}_4$ $[\text{M}+\text{H}]^+$: 205.1448, found: 205.1440

Synthesis of *rac*-2-[(4*aR*,5*R*,8*aR*)-1-(3,5-dinitrobenzoyl)decahydroquinolin-5-yl]acetonitrile (133**).**

A solution of compound **131** (80 mg, 0.39 mmol) in dry MeOH (12 mL) was heated in a microwave reactor at 140°C for 3 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude material was dissolved in absolute ethanol (8 mL), cooled to 0°C and sodium borohydride (30 mg, 0.78 mmol) was added. After 45 min the reaction mixture was quenched with saturated NH_4Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH_2Cl_2 (3 X 30 mL). The combined organic layers were dried with MgSO_4 , filtered and concentrated in vacuo. The crude oil was dissolved in CH_2Cl_2 (8 mL), cooled to 0°C and Et_3N (0.11 mL, 0.78 mmol) and 3,5-dinitrobenzoyl chloride (137 mg, 0.59 mmol) were added sequentially. After stirring at room temperature for 10 hours the reaction mixture was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO_4 , filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) to afford compound **133** (72 mg, 50%, 3 steps) as a yellow solid.



(*m*, 1H, H-4 β).

^1H -NMR (400 MHz, CDCl_3): δ 9.08 (t, 1H, J = 2.1 Hz, Ar-H), 8.57 (d, 2H, J = 2.1 Hz, Ar-H), 3.65 (td, 1H, J = 10.9, J = 3.3 Hz, H-8 α), 3.46 (ddd, 1H, $J_{2\alpha,2\beta}$ = 14.0, $J_{2\alpha,3\alpha}$ = 10.7, $J_{2\alpha,3\beta}$ = 5.6, H-2 α), 3.30 (ddd, 1H, $J_{2\beta,2\alpha}$ = 14.0, $J_{2\beta,3\beta}$ = 6.4, $J_{2\beta,3\alpha}$ = 3.0 Hz, H-2 β), 2.47 (dd, 2H, J = 4.9, J = 1.7 Hz, 2H-9), 2.29 (*m*, 1H, H-8 α), 2.04-1.86 (*m*, 3H, H-4 α , H-6 α and H-7 α), 1.85-1.63 (*m*, 3H, H-4 α and 2H-3), 1.62-1.53 (*m*, 3H, H-5, H-7 β and H-8 β), 1.43 (*m*, 1H, H-6 β), 1.24

^{13}C -NMR (100 MHz, CDCl_3): δ 166.4 (C=O), 148.6 (2C, Ar-C), 140.4 (Ar-C), 127.4 (2C, Ar-C), 119.7 (Ar-C), 118.0 (CN), 60.8 (C-8a), 42.8 (C-2), 41.0 (C-4a), 38.9 (C-5), 32.1 (C-6), 29.6 (C-8), 24.2 (C-7), 23.6 (C-3), 22.9 (C-4), 21.6 (C-9).

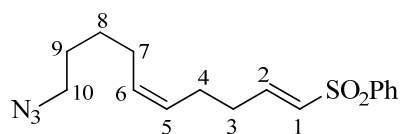
FTIR (KBr) ν_{max} : 3101, 2933, 2863, 2245, 1731, 1633, 1538, 1463, 1428, 1345, 1274, 1173, 1131, 1080, 917, 731 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{18}\text{H}_{21}\text{N}_4\text{O}_5$ $[\text{M}+\text{H}]^+$: 373.1506, found: 373.1506

Mp: 65-68°C

Synthesis of [(1*E*,5*Z*)-10-azidodeca-1,5-dien-1-yl]sulfonyl}benzene (**134**).

To a solution of methyl phenyl sulfone (220 mg, 1.41 mmol) in THF (30 mL), cooled at -78°C, *n*-BuLi (0.97 mL, 1.6 M in hexane, 1.55 mmol) was added. The solution was stirred for 30 minutes and a solution of **127** (280 mg, 1.55 mmol) in THF (15 mL) was added at -78°C. The resulting solution was stirred for 30 minutes and then warmed to room temperature over 2 hours. The reaction mixture was quenched with a saturated solution of NH_4Cl (15 mL) and extracted with EtOAc (3 X 30 mL). The organic layer was dried with MgSO_4 , filtered and concentrated in vacuo. The crude alcohol was dissolved in CH_2Cl_2 (25 mL) at 0°C. Et_3N (1.96 mL, 14.1 mmol) and methanesulfonyl chloride (0.16 mL, 2.12 mmol) were added. After the mixture was stirred for 2 hours at room temperature a saturated solution of NH_4Cl (15 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 X 30 mL) and the combined organic layers were dried with MgSO_4 , filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, gradient from hexanes to 70:30 hexanes/EtOAc) yielded compound **134** as a colorless oil (288 mg, 64%, 2 steps).



^1H -NMR (300 MHz, CDCl_3): δ 7.84 (m, 2H, Ar-H), 7.58 (m, 1H, Ar-H), 7.50 (m, 2H, Ar-H), 6.94 (dt, 1H, $J_{2,1} = 15.1$, $J_{2,3} = 6.6$ Hz, H-2), 6.32 (dt, 1H, $J_{1,2} = 15.1$, $J_{1,3} = 1.5$ Hz, H-1), 5.33 (m, 2H, H-5 and H-6), 3.23 (t, 2H, $J_{10,9} = 6.8$ Hz, 2H-10), 2.26 (m, 2H, 2H-3), 2.19 (m, 2H, 2H-4), 2.00 (m, 2H, 2H-7), 1.56 (m, 2H, 2H-9), 1.40 (m, 2H, 2H-8).

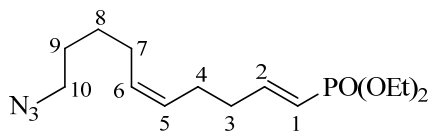
^{13}C -NMR (75 MHz, CDCl_3): δ 146.4 (C-2), 140.7 (Ar-C), 133.4 (Ar-C), 131.0 (C-6), 130.9 (C-1), 129.3 (2C, Ar-C), 127.8 (C-5), 127.7 (2C, Ar-C), 51.4 (C-10), 31.5 (C-3), 28.5 (C-9), 26.8 (C-8), 26.7 (C-7), 25.5 (C-4).

FTIR (neat) ν_{max} : 3064, 3009, 2935, 2861, 2096, 1627, 1447, 1319, 1289, 1147, 1087, 828, 752, 716, 688 cm^{-1} .

HRMS-ESI (m/z): calcd for C₁₆H₂₂N₃O₂S [M+H]⁺: 320.1427, found: 320.1425

Synthesis of diethyl [(1*E*,5*Z*)-10-azidodeca-1,5-dien-1-yl]phosphonate (135**).**

Tetraethylmethylenediphosphonate (393 mg, 1.36 mmol) in dry THF (5 mL) was added to a suspension of NaH (55 mg, 1.36 mmol) in dry THF (15 mL) at 0°C. After 30 minutes a solution of aldehyde **127** (165 mg, 0.91 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 0°C for 90 minutes. The reaction was warmed to room temperature and then quenched with saturated NH₄Cl. The mixture was extracted with EtOAc (3 X 30 mL) and the organic layer was dried with MgSO₄, filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography (silica gel, gradient from hexanes to 40:60 hexanes/EtOAc) to obtain compound **135** as a colorless oil (254 mg, 89%).



¹H-NMR (300 MHz, CDCl₃): δ 6.75 (ddt, 1H, *J*_{2,P} = 21.9, *J*_{2,1} = 17.2, *J*_{2,3} = 6.2 Hz, H-2), 5.65 (ddt, 1H, *J*_{1,P} = 21.0, *J*_{1,2} = 17.2, *J*_{1,3} = 1.5 Hz, H-1), 5.36 (m, 2H, H-5 and H-6), 4.06 (m, 4H, OCH₂CH₃), 3.26 (t, 2H, *J*_{10,9} = 6.8 Hz, 2H-10), 2.30-2.12 (m, 4H, 2H-4 and 2H-3), 2.04 (m, 2H, 2H-7), 1.59 (m, 2H, 2H-9), 1.43 (m, 2H, 2H-8), 1.31 (t, 6H, *J* = 7.1, OCH₂CH₃).

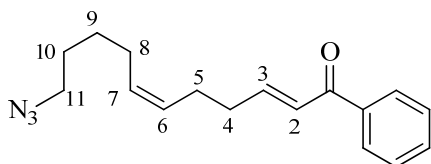
¹³C-NMR (75 MHz, CDCl₃): δ 153.0 (d, *J*_{C,P} = 4 Hz, C-2), 130.4 (C-6), 128.6 (C-5), 117.4 (d, *J*_{C,P} = 188 Hz, C-1), 61.7 (2C, OCH₂CH₃), 51.5 (C-10), 34.2 (d, *J*_{C,P} = 22 Hz, C-3), 28.6 (C-9), 26.9 (C-8), 26.8 (C-7), 25.7 (C-4), 16.5 (2C, d, *J*_{C,P} = 6 Hz, OCH₂CH₃).

FTIR (neat) ν_{max}: 2982, 2935, 2864, 2096, 1633, 1455, 1444, 1392, 1368, 1352, 1647, 1165, 1098, 1055, 1028, 963, 841 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₄H₂₇N₃O₃P [M+H]⁺: 316.1785, found: 316.1769.

Synthesis of (2*E*,6*Z*)-11-azido-1-phenylundeca-2,6-dien-1-one (136**).**

To a solution of **127** (180 mg, 0.99 mmol) in CH₂Cl₂ (20 mL) was added 1-phenyl-2-(triphenylphosphoranylidene)ethanone (1130 mg, 2.97 mmol) at room temperature and the mixture was stirred for 3 days. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) to provide compound **136** as a colorless oil (224 mg, 80%).



¹H-NMR (300 MHz, CDCl₃): δ 7.92 (m, 2H, Ar-H), 7.55 (m, 1H, Ar-H), 7.46 (m, 2H, Ar-H), 7.04 (dt, 1H, *J*_{3,2} = 15.4, *J*_{3,4} = 6.5 Hz, H-3), 6.89 (dt, 1H, *J*_{2,3} = 15.4,

$J_{2,4} = 1.3$ Hz, H-2), 5.41 (m, 2H, H-6 and H-7), 3.26 (t, 2H, $J_{11,10} = 6.8$ Hz, 2H-11), 2.37 (m, 2H, 2H-4), 2.27 (m, 2H, 2H-5), 2.08 (m, 2H, 2H-8) 1.60 (m, 2H, 2H-10), 1.45 (m, 2H, 2H-9).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 190.0 (C=O), 149.1 (C-3), 138.1 (Ar-C), 132.8 (Ar-C), 130.5 (C-7), 128.8 (C-6), 128.7 (4C, Ar-C), 126.4 (C-2), 51.5 (C-11), 33.0 (C-4), 28.6 (C-10), 26.9 (C-8), 26.8 (C-9), 26.1 (C-5).

FTIR (neat) ν_{max} : 3008, 2936, 2861, 2096, 1671, 1652, 1622, 1598, 1579, 1448, 1349, 1287, 1231, 976, 695 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{17}\text{H}_{22}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 284.1757, found: 284.1762

Synthesis of (5*E*,9*Z*)-14-azidotetradeca-5,9-dien-4-one (**137**).

A suspension of NaH (66 mg of 60% in mineral oil, 1.66 mmol) in dry THF (20 mL) was cooled to -78°C . Dimethyl (2-oxopentyl)phosphonate (322 mg, 1.66 mmol) dissolved in THF (10 mL) was added dropwise and the reaction mixture was stirred for 20 minutes at -78°C and 20 minutes at 0°C . Then a solution of **127** (150 mg, 0.83 mmol) in dry THF (10 mL) was added dropwise and the mixture was stirred for 30 minutes at 0°C . The reaction was warmed to room temperature and after 1 hour and 30 minutes it was quenched with water and extracted with Et_2O (3 X 30 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/ EtOAc) yielded compound **137** as a colorless oil (180 mg, 88%).

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 6.81 (dt, 1H, $J_{6,5} = 15.9$, $J_{6,7} = 6.6$ Hz, H-6), 6.10 (dt, 1H, $J_{5,6} = 15.9$, $J_{5,7} = 1.5$ Hz, H-5), 5.39 (m, 2H, H-9 and H-10), 3.27 (t, 2H, $J_{14,13} = 6.8$ Hz, 2H-14), 2.50 (t, 2H, $J_{3,2} = 7.3$ Hz, 2H-3), 2.24 (m, 4H, 2H-7 and 2H-8), 2.06 (m, 2H, 2H-11), 1.62 (m, 4H, 2H-2 and 2H-13), 1.44 (m, 2H, 2H-12), 0.93 (t, 3H, $J_{1,2} = 7.4$ Hz, CH_3).

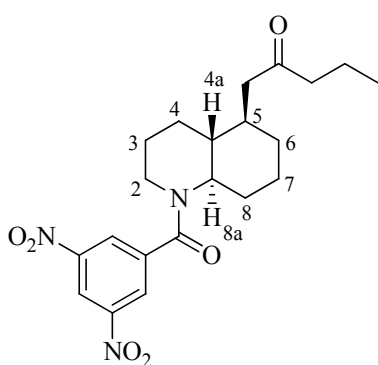
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 200.8 (C=O), 146.3 (C-6), 130.8 (C-5), 130.4 (C-10), 128.7 (C-9), 51.5 (C-14), 42.2 (C-3), 32.5 (C-7), 28.6 (C-13), 26.9 (C-11), 26.8 (C-12), 26.0 (C-8), 17.9 (C-2), 14.0 (C-1).

FTIR (neat) ν_{max} : 3009, 2963, 2935, 2874, 2097, 1697, 1675, 1630, 1458, 1272, 978 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{14}\text{H}_{24}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 250.1914, found: 250.1910

Synthesis of *rac*- 1-[(4a*R*,5*R*,8a*R*)-1-(3,5-dinitrobenzoyl)decahydroquinolin-5-yl]pentan-2-one (139).

A solution of compound **137** (90 mg, 0.36 mmol) in dry MeOH (12 mL) was heated in a microwave reactor at 140°C for 3 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude material was dissolved in absolute ethanol (8 mL), cooled to 0°C and sodium borohydride (16 mg, 0.43 mmol) was added. After 1 hour the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 X 30 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated in vacuo. The crude oil was dissolved in CH₂Cl₂ (8 mL), cooled to 0°C and Et₃N (0.1 mL, 0.72 mmol) and 3,5-dinitrobenzoyl chloride (124 mg, 0.54 mmol) were added sequentially. After stirring at room temperature for 10 hours the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 X 15 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) to afford compound **133** (38 mg, 25%, 3 steps) as a yellow solid.



¹H-NMR (400 MHz, CDCl₃): δ 9.07 (td, 1H, *J* = 2.1, *J* = 0.5 Hz, Ar-H), 8.57 (dd, 2H, *J* = 2.1, *J* = 0.5 Hz, Ar-H), 3.59 (td, 1H, *J* = 10.9, *J* = 3.3 Hz, H-8a), 3.42 (ddd, 1H, *J*_{2α,2β} = 13.9, *J*_{2α,3α} = 10.4, *J*_{2α,3β} = 5.5, H-2α), 3.28 (ddd, 1H, *J*_{2β,2α} = 13.9, *J*_{2β,3β} = 6.4, *J*_{2β,3α} = 3.4 Hz, H-2β), 2.58 (dd, 1H, *J* = 16.4, *J* = 4.3 Hz, CHCH₂CO), 2.38 (m, 2H, CH₂CH₂CH₃), 2.23 (m, 2H, CHCH₂CO and H-8α), 1.90-1.45 (m, 11H, 2H-3, H-4α, H-4a, H-5, H-6α, 2H-7, H-8β, CH₂CH₂CH₃), 1.16 (m, 1H, H-4β), 1.08 (m, 1H, H-6β), 0.92 (t, 3H, *J* = 7.4 Hz, CH₂CH₂CH₃).

¹³C-NMR (100 MHz, CDCl₃): δ 210.5 (C=O, ketone), 166.3 (C=O, amide), 148.6 (2C, Ar-C), 140.6 (Ar-C), 127.4 (2C, Ar-C), 119.5 (Ar-C), 61.8 (C-8a), 46.8 (CHCH₂CO), 45.7 (CH₂CH₂CH₃), 43.3 (C-2), 42.4 (C-4a), 38.3 (C-5), 32.9 (C-6), 30.0 (C-8), 24.7 (C-7), 24.0 (C-3), 23.7 (C-4), 17.3 (CH₂CH₂CH₃), 13.9 (CH₂CH₂CH₃).

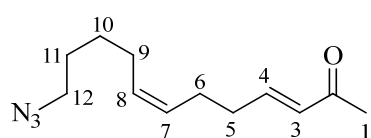
FTIR (neat) ν_{max}: 3103, 2934, 2872, 1723, 1715, 1633, 1543, 1463, 1430, 1344, 1276, 1172, 1078, 918, 730 cm⁻¹.

HRMS-ESI (m/z): calcd for C₂₁H₂₈N₃O₆ [M+H]⁺: 418.1973, found: 418.1980

Mp: 58-60°C

Synthesis of (3*E*,7*Z*)-12-azidododeca-3,7-dien-2-one (140).

To a solution of **127** (150 mg, 0.83 mmol) in CH₂Cl₂ (20 mL) was added 1-(triphenylphosphoranylidene)-2-propanone (793 mg, 2.49 mmol) at room temperature and the mixture was stirred for 3 days. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 85:15 hexanes/EtOAc) to provide compound **140** as a colorless oil (145 mg, 79%).



¹H-NMR (300 MHz, CDCl₃): δ 6.79 (dt, 1H, *J*_{4,3} = 15.9, *J*_{4,5} = 6.5 Hz, H-4), 6.08 (dt, 1H, *J*_{3,4} = 15.9, *J*_{3,5} = 1.5 Hz, H-3), 5.39 (m, 2H, H-7 and H-8), 3.27 (t, 2H, *J*_{12,11} = 6.8 Hz, 2H-12), 2.24 (s, 3H, CH₃), 2.23 (m, 4H, 2H-5 and 2H-6), 2.05 (m, 2H, 2H-9), 1.60 (m, 2H, 2H-11), 1.45 (m, 2H, 2H-10).

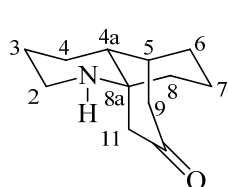
¹³C-NMR (75 MHz, CDCl₃): δ 198.7 (C=O), 147.6 (C-4), 131.7 (C-3), 130.5 (C-8), 128.6 (C-7), 51.5 (C-12), 32.6 (C-5), 28.6 (C-11), 27.0 (CH₃), 26.9 (C-9), 26.8 (C-10), 26.0 (C-6).

FTIR (neat) *v*_{max}: 3008, 2936, 2861, 2095, 1698, 1675, 1626, 1454, 1436, 1359, 1253, 977, 723 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₂H₂₀N₃O [M+H]⁺: 222.1601, found: 222.1600

Cyclization of 140. Synthesis of *rac*-(4*aR*,5*S*,8*aS*)-hexahydro-1*H*-5,8*a*-propanoquinolin-7(8*H*)-one (143).

A solution of compound **140** (75 mg, 0.34 mmol) in dry MeOH (12 mL) was heated in a microwave reactor at 140°C for 3 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude material was purified by flash chromatography (silica gel, gradient from CH₂Cl₂ to 9:1 CH₂Cl₂/MeOH) to obtain compound **143** as a pale brown oil (38 mg, 58%).



¹H-NMR (400 MHz, CDCl₃): δ 3.00 (d, 1H, *J*_{11α,11β} = 16.9 Hz, H-11α), 2.89 (m, 2H, 2H-2), 2.45 (dd, 1H, *J*_{9α,9β} = 17.1, *J*_{9α,5} = 6.3 Hz, H-9α), 2.19 (d, 1H, *J*_{9β,9α} = 17.1 Hz, H-9β), 2.09 (m, 2H, H-5 and H-11β), 1.82-1.75 (m, 1H, H-3α), 1.70-1.53 (m, 9H, H-3β, 2H-4, H-4a, 2H-6, 2H-7 and H-8α), 1.46 (m, 1H, H-8β).

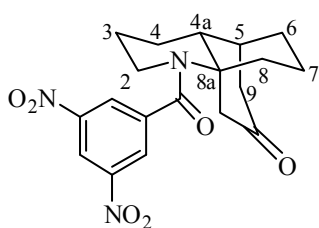
¹³C-NMR (100 MHz, CDCl₃): δ 212.8 (C=O), 55.3 (C-8a), 45.6 (C-11), 44.1 (C-5), 42.0 (C-8), 41.8 (C-9), 40.8 (C-2), 35.5 (C-4a), 33.4 (C-6), 26.9 (C-3), 25.5 (C-4), 19.4 (C-7).

FTIR (neat) *v*_{max}: 2932, 2856, 1704, 1463, 1322, 1275, 1086, 725 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₂H₂₀NO [M+H]: 194.1539, found: 194.1541

Synthesis of *rac*-(4a*R*,5*S*,8a*S*)-1-(3,5-dinitrobenzoyl)hexahydro-1*H*-5,8a-propanoquinolin-7(8*H*)-one (144).

A solution of compound **140** (75 mg, 0.34 mmol) in dry MeOH (12 mL) was heated in a microwave reactor at 140°C for 3 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude oil was dissolved in CH₂Cl₂ (8 mL), cooled to 0°C and Et₃N (0.9 mL, 0.68 mmol) and 3,5-dinitrobenzoyl chloride (117 mg, 0.51 mmol) were sequentially added. After stirring at room temperature for 10 hours the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were washed with brine, dried with MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from hexanes to 1:1 hexanes/EtOAc) to afford compound **144** (57 mg, 43%, 2 steps) as a yellow solid. The relative stereochemistry of **144** was confirmed by X-ray crystallographic analysis.¹⁰



¹H-NMR (400 MHz, CDCl₃): δ 9.07 (t, 1H, J = 2.1 Hz, Ar-H), 8.59 (d, 2H, J = 2.1 Hz, Ar-H), 3.57 (m, 2H, H-2 α and H-11 α), 3.26 (m, 1H, H-8 α), 3.14 (m, 1H, H-2 β), 2.67 (d, 1H, J = 17.1 Hz, H-11 β), 2.60 (dd, 1H, $J_{9\alpha,9\beta}$ = 17.6, J = 6.8 Hz, H-9 α), 2.28 (m, 2H, H-4 α and H-9 β), 2.12 (m, 1H, H-5), 1.86 (m, 2H, 2H-3), 1.80-1.71 (m, 5H, 2H-4, 2H-6 and H-7 α), 1.54 (m, 1H, H-8 β), 1.47 (m, 1H, H-7 β).

¹³C-NMR (100 MHz, CDCl₃): δ 207.5 (C=O, ketone), 167.9 (C=O, amide), 148.7 (Ar-C), 141.7 (Ar-C), 127.5 (2C, Ar-C), 119.8 (2C, Ar-C), 62.1 (C-8a), 44.9 (C-2), 44.5 (C-11), 41.6 (2C, C-9 and C-5), 36.1 (C-8), 35.5 (C-4a), 33.2 (C-6), 23.7 (C-3), 23.4 (C-4), 19.8 (C-7).

FTIR (KBr) ν_{\max} : 3101, 2935, 2875, 1706, 1637, 1543, 1459, 1407, 1344, 1268, 1149, 1079, 919, 731 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₉H₂₂N₃O₆ [M+H]⁺: 388.1503, found: 388.1504

Mp: 218-220°C

¹⁰ Los datos de difracción de rayos X del compuesto **144** se encuentran en el anexo II.

Capítulo 3

APROXIMACIÓN A LA SÍNTESIS DE ALCALOIDES DE *LYCOPodium*

3.1.-INTRODUCCIÓN Y ANTECEDENTES.

Los alcaloides del género *Lycopodium* son una gran familia de compuestos que han suscitado mucho interés desde hace más de 100 años debido a su complejidad estructural e interesantes propiedades biológicas.¹ De las más de 500 especies de *Lycopodia* que se conocen, únicamente se han estudiado algo más de 50 hasta la fecha y han sido descritos más de 250 alcaloides de este tipo. Actualmente su clasificación se realiza en base a su estructura tal y como plantearon Ayer y Trifonov en 1964,² que los separaron en cuatro grupos: los de tipo lycopodina, licodina, fawcettimina y un cuarto grupo heterogéneo, uno de cuyos representantes es la phlegmarina (Figura 3.1).

Desde hace mucho tiempo son conocidas además las propiedades de estos compuestos y ya en la medicina tradicional china eran empleados para tratar contusiones, esguinces o enfermedades como la esquizofrenia.³ Además estos alcaloides poseen actividad antipirética⁴ y anticolinesterasa⁵ y ha quedado demostrado que ejercen un efecto positivo en el aprendizaje y la memoria.⁶ Debido a estas interesantes propiedades muchos grupos han dedicado sus esfuerzos a la síntesis de estos compuestos y en los últimos años se han publicado numerosas síntesis totales de diferentes alcaloides de *Lycopodium*.⁷

¹ a) X. Ma, D. R. Gang, *Nat. Prod. Rep.* **2004**, *21*, 752-772; b) J. Kobayashi, H. Morita, In *The Alkaloids: Chemistry and Biology*; Ed. G. A. Cordell, Elsevier: San Diego, CA, **2005**; Vol. 61, pp 1-57; c) Y. Hirasawa, J. Kobayashi, H. Morita, *Heterocycles*, **2009**, *77*, 679-729; d) M. Kitajima, H. Takayama, *Top. Curr. Chem.* **2012**, *309*, 1-31.

² W. A. Ayer and L. S. Trifonov, in *Lycopodium Alkaloids*, Academic Press, San Diego, **1994**.

³ *Jiangsu New Medical College: The Dictionary of traditional Chinese medicine*, Shanghai Sci-Tech Press, Shanghai, **1985**.

⁴ M. Nikonorow, *Acta Pol. Pharm.* **1939**, *3*, 23-56.

⁵ M. G. Ortega, A. M. Agnese, J. L. Cabrera, *Phytomedicine*, **2004**, *11*, 539-543.

⁶ a) X. C. Tang, Y. F. Han, X. P. Chen, X. D. Zhu, *Acta Pharmacol. Sin.* **1986**, *7*, 507-511; b) J. S. Liu, Y. L. Zhu, C. M. Yu, Y. Z. Zhou, Y. Y. Han, F. W. Wu, B. F. Qi, *Can. J. Chem.* **1986**, *64*, 837-839; c) X. D. Zhu and X. C. Tang, *Yaoxue Xuebao*, **1987**, *22*, 812-817.

⁷ a) B. L. Nilsson, L. E. Overman, J. R. Alaniz, J. M. Rohde, *J. Am. Chem. Soc.* **2008**, *130*, 11297-11299; b) A. Chandra, J. A. Pigza, J.-S. Han, D. Mutnick, J. N. Johnston, *J. Am. Chem. Soc.* **2009**, *131*, 3470-3471; c) H. Yang, R. G. Carter, *J. Org. Chem.* **2010**, *75*, 4929-4938; d) K. M. Laemmerhold, B. Breit, *Angew. Chem. Int. Ed.* **2010**, *49*, 2367-2370; e) C. Tsukano, L. Zhao, Y. Takemoto, M. Hirama, *Eur. J. Org. Chem.* **2010**, 4198-4200; f) V. Bisai, R. Sarpong, *Org. Lett.* **2010**, *12*, 2551-2553; g) R. A. Altman, B. L. Nilsson, L. E. Overman, J. R. Alaniz, J. M. Rohde, V. Taupin, *J. Org. Chem.* **2010**, *75*, 7519-7534; h) X. Cheng, S. P. Waters, *Org. Lett.* **2010**, *12*, 205-207; i) B. H. Wolfe, A. H. Libby, R. S. Al-awar, C. J. Foti, D. L. Comins, *J. Org. Chem.* **2010**, *75*, 8564-8570; j) Y. Nakamura, A. M. Burke, S. Kotani, J. W. Ziller, S. D. Rychnovsky, *Org. Lett.* **2010**, *12*, 72-75; k) B. B. Liau, M. D. Shair, *J. Am. Chem. Soc.* **2010**, *132*, 9594-9595; l) C. Yuan, C.-T. Chang, A. Axelrod, D. Siegel, *J. Am. Chem. Soc.* **2010**, *132*, 5924-5925; m) D. F. Fischer, R. Sarpong, *J. Am. Chem. Soc.* **2010**, *132*, 5926-5927; n) J. Ramharter, W. Weinstabl, J. Mulzer, *J. Am. Chem. Soc.* **2010**, *132*, 14338-14339; o) T. Nishimura, A. K. Unni, S. Yokoshima, T. Fukuyama, *J. Am. Chem. Soc.* **2011**, *133*, 418-419; p) K. Nakahara, K. Hirano, R. Maehata, Y. Kita, H. Fujioka, *Org. Lett.* **2011**, *13*, 2015-2017; q) G. Barbe, D. Fiset, A. B. Charette, *J. Org. Chem.* **2011**, *76*, 5354-5362; r) Y.-R. Yang, L. Shen, J.-Z. Huang, T. Xu, K. Wei, *J. Org. Chem.* **2011**, *76*, 3684-3690; s) A. Nakayama, N. Kogure, M. Kitajima, H. Takayama, *Angew. Chem. Int. Ed.* **2011**, *50*, 8025-8028; t) X.-M. Zhang, Y. Tu, F.-M. Zhang, H. Shao, X. Meng, *Angew. Chem. Int. Ed.* **2011**, *50*, 3916-3919; u) R. A. Murphy, R. Sarpong, *Org. Lett.* **2012**, *14*, 632-635; v) H. Lin, R. Causey, G. E. Garcia, B. B. Snider, *J. Org. Chem.* **2012**, *77*, 7143; w) L. Houhua, X. Wang, X. Lei, *Angew. Chem. Int. Ed.* **2012**, *51*, 491-495; x) N. Shimada, Y. Abe, S. Yokoshima, T. Fukuyama, *Angew. Chem. Int. Ed.* **2012**, *51*, 1-4; y) X.-M. Zhang, H. Shao, Y.-Q. Tu, F.-M. Zhang, S.-H. Wang, *J. Org. Chem.* **2012**, *77*, 8174-8181; z) H. M. Ge, L.-D. Zhang, R. X. Tan, Z.-J. Yao, *J. Am. Chem. Soc.* **2012**, *134*, 12323-12325.

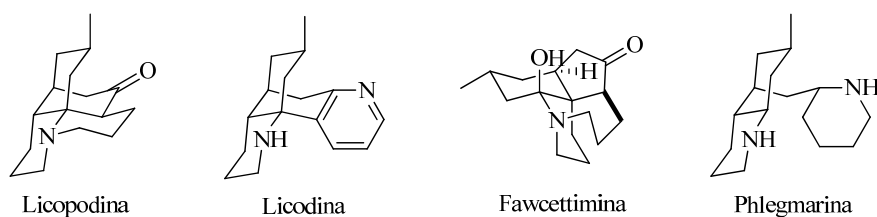


Figura 3.1. Alcaloides de *Lycopodium* más representativos.

De todos ellos la licopodina es el más abundante. Fue aislada por primera vez en 1881 por Bödeker,⁸ pero no fue hasta 50 años más tarde cuando se publicó su fórmula molecular.⁹ La estructura y estereoquímica fue dilucidada por Ayer e Iverach en 1962¹⁰ y un poco más tarde se estableció su configuración absoluta por difracción de rayos X.¹¹ La síntesis total de este alcaloide ha sido también el objetivo de varios grupos de investigación y como resultado hasta ahora se han publicado en total nueve síntesis totales de la licopodina^{12,13,14,15,16,17,18,19,20} y dos síntesis formales^{21,22} de las cuales se destacan a continuación las más importantes.

Las dos primeras aparecieron simultáneamente en 1968 y pertenecen a los grupos de Stork¹² y Ayer.¹³ La síntesis de Stork parte del *m*-metoxibenzaldehído que es transformado en el intermedio **I** en seis etapas (Esquema 3.1). Posteriormente empleando acrilamida se llega al compuesto **II** que en medio ácido cicla para dar el tetraciclo **III**. A continuación se elimina el carbonilo de la amida, se reduce el anillo aromático y se protege la amina formando un carbamato para obtener el intermedio **IV**. El siguiente paso es una ozonolisis con posterior eliminación del aldehído α,β -insaturado formado llegando así al compuesto **V**. Finalmente se obtiene la licopodina mediante eliminación del grupo protector de la amina y formación de la correspondiente lactama, reducción de la misma y reoxidación de la dihidrolicopodina obtenida.

⁸ K. Bodeker, *Justus Liebigs Ann. Chem.* **1881**, 208, 363-367.

⁹ O. Achmatowicz, W. Uzieblo, *Rocz. Chem.* **1938**, 18, 88-95.

¹⁰ W. A. Ayer, G. G. Iverach, *Tetrahedron Lett.* **1962**, 87-92.

¹¹ M. Hague, D. Rogers, *J. Chem. Soc. Perkin Trans.* **1975**, 2, 93-98.

¹² G. Stork, A. Kretschmer, R. H. Schlessinger, *J. Am. Chem. Soc.* **1968**, 90, 1647-1648.

¹³ W. A. Ayer, W. R. Bowman, T. C. Joseph, P. Smith, *J. Am. Chem. Soc.* **1968**, 90, 1648-1650.

¹⁴ S.-W. Kim, Y. Bando, Z. Horii, *Tetrahedron Lett.* **1978**, 2293-2294.

¹⁵ a) C. H. Heathcock, E. Kleinman, E. S. Binkley, *J. Am. Chem. Soc.* **1978**, 100, 8036-8037; b) C. H. Heathcock, E. Kleinman, E. S. Binkley, *J. Am. Chem. Soc.* **1982**, 104, 1054-1068.

¹⁶ D. Schuman, H. J. Müller, A. Naumann, *Liebigs Ann. Chem.* **1982**, 1700-1705.

¹⁷ E. Wenkert, C. A. Broka, *J. Chem. Soc. Chem. Commun.* **1984**, 714-715.

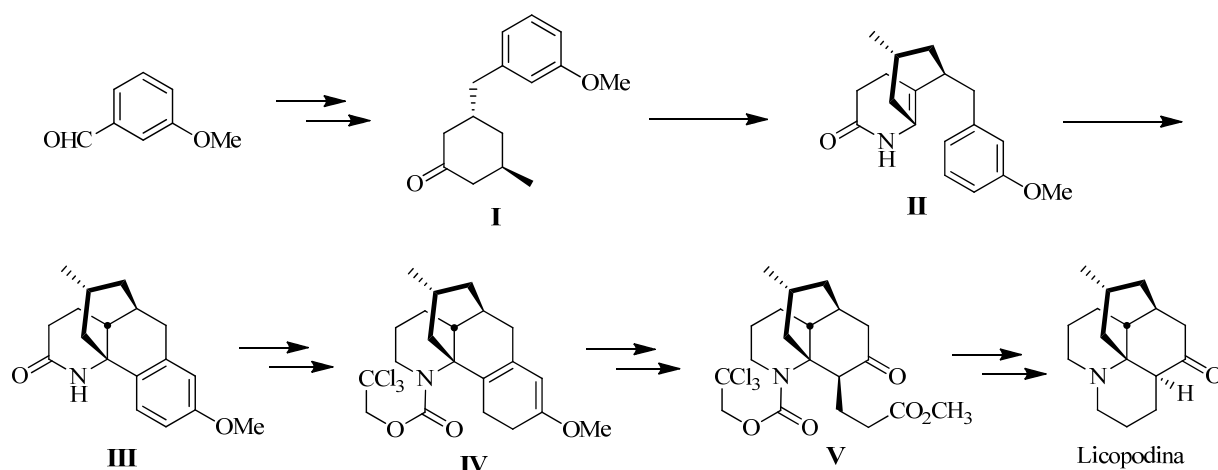
¹⁸ a) G. A. Kraus, Y.-S. Hon, *J. Am. Chem. Soc.* **1985**, 107, 4341-4342; b) G. A. Kraus, Y.-S. Hon, *Heterocycles*, **1987**, 25, 377-386.

¹⁹ P. A. Grieco, Y. Dai, *J. Am. Chem. Soc.* **1998**, 120, 5128-5129.

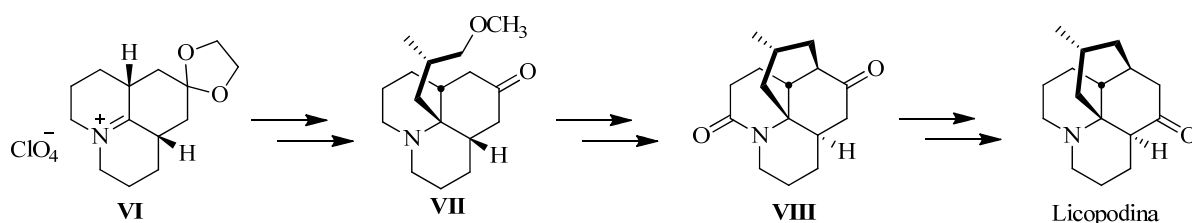
²⁰ a) H. Yang, R. G. Carter, L. N. Nakharov, *J. Am. Chem. Soc.* **2008**, 130, 9238-9239; b) Y. Hang, R. G. Carter, *J. Org. Chem.* **2010**, 75, 4929-4938.

²¹ A. Padwa, M. A. Brodney, J. P. Marino, S. M. Sheehan, *J. Org. Chem.* **1997**, 62, 78-87.

²² M. Mori, K. Hori, M. Akashi, M. Hori, Y. Sato, M. Nishida, *Angew. Chem. Int. Ed.* **1998**, 37, 636-637.

Esquema 3.1. Síntesis de la lycopodina de Stork.¹²

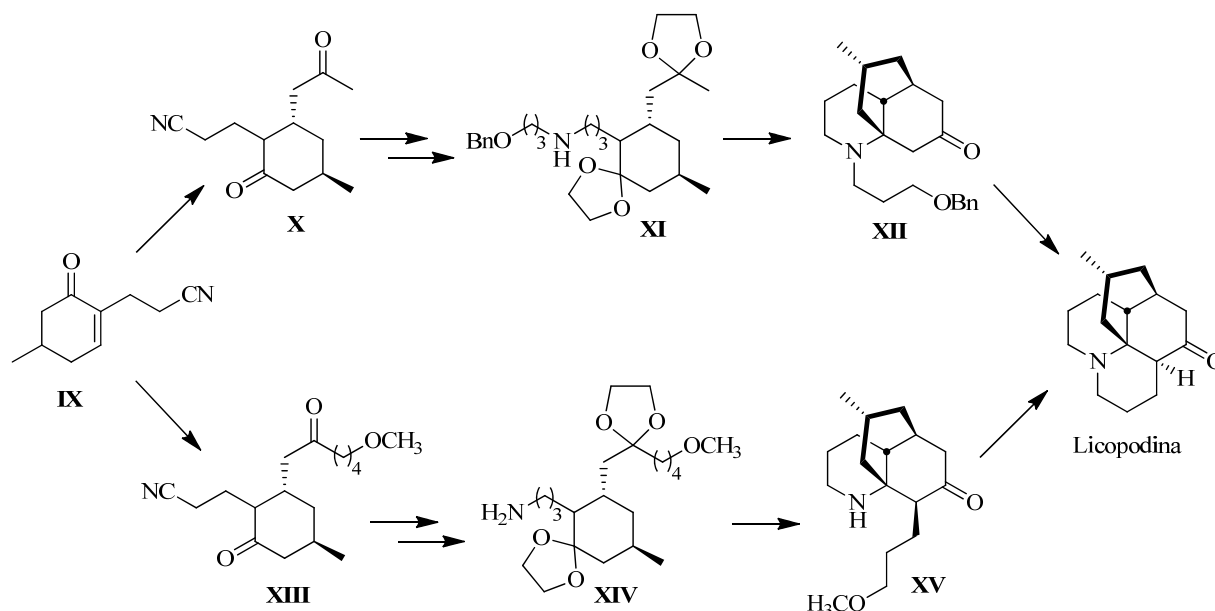
En cuanto a la síntesis de Ayer,¹³ éste utiliza como punto de partida el compuesto ya conocido **VI**²³ que por reacción con el magnesiano del 1-cloro-2-metil-3-metoxipropano e hidrólisis del acetal permite llegar al compuesto **VII** (Esquema 3.2). Los siguientes pasos son una epimerización en el carbono C-4 y oxidación a la lactama. Posteriormente se lleva a cabo una transformación del grupo metoxi en un mesilato para proceder a la ciclación en medio básico y poder aislar el intermedio **VIII**. Finalmente se obtiene la lycopodina reduciendo la lactama y reoxidando el alcohol obtenido a la cetona que a través de un diosfenol da lugar a la lycopodina.

Esquema 3.2. Síntesis de la lycopodina de Ayer.¹³

Otro grupo que dedicó muchos esfuerzos a la síntesis de este tipo de alcaloides fue el grupo de Heathcock. En 1978 publicaron la síntesis de la lycopodina y cuatro años más tarde la síntesis de la licodina y licodolina, dos alcaloides muy similares.¹⁵ La estrategia planteada por este grupo se basa en una reacción de Mannich intramolecular. Así en el caso de la lycopodina presentan dos rutas parecidas que parten ambas del compuesto **IX** (Esquema 3.3). A partir de aquí por adición conjugada llegan a los compuestos **X** o **XIII**, cuyos grupos carbonilo son protegidos para posteriormente transformar el grupo nitrilo en una amina secundaria o primaria, según la ruta empleada. Posteriormente por tratamiento con HCl/MeOH a reflujo tiene lugar la desprotección de los grupos carbonilo y reacción de Mannich

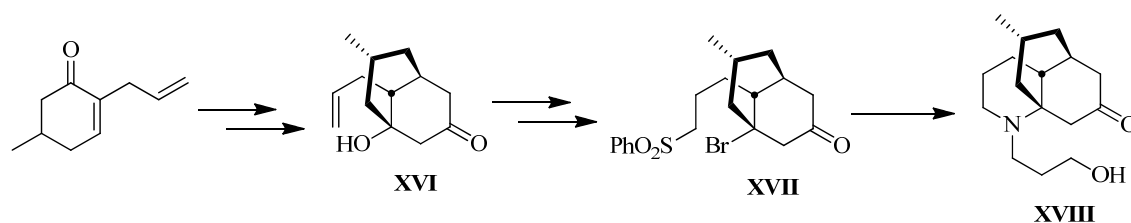
²³ W. A. Ayer, W. R. Bowman, G. A. Cooke, A. C. Soper, *Tetrahedron Lett.* **1966**, 18, 2021-2026.

llegando a las correspondientes aminas **XII** y **XV**. Finalmente se elimina el grupo bencilo del compuesto **XII** y se oxida al aldehído mediante una reacción de Oppenauer. Bajo estas condiciones fuertemente básicas tiene lugar además la condensación aldólica y deshidratación del alcohol aislándose la correspondiente enona que es hidrogenada para obtener la lycopodina. Por otro lado el intermedio **XV** también da lugar a la lycopodina mediante ciclación empleando HBr/HOAc y posterior basificación.



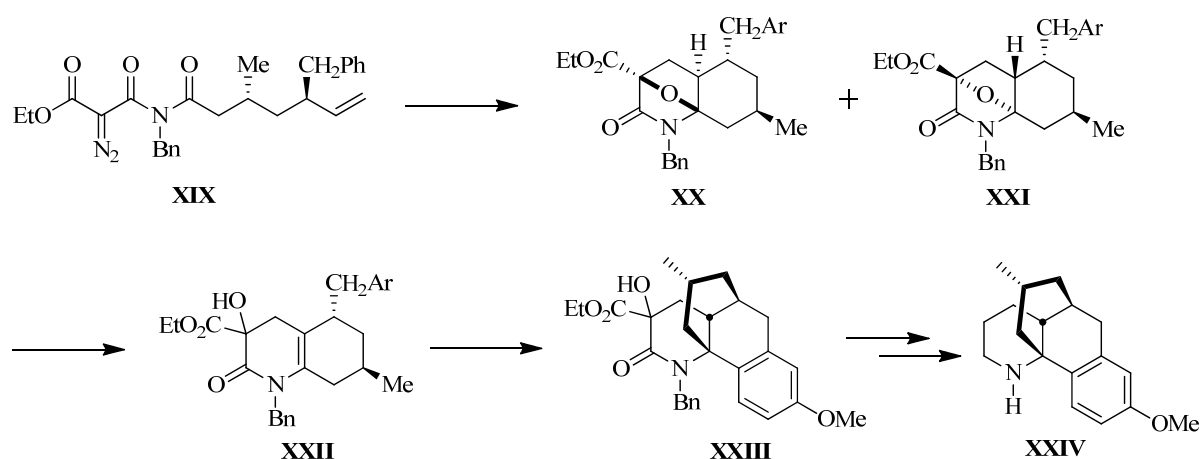
Esquema 3.3. Síntesis de la lycopodina de Heathcock.¹⁵

En 1987 apareció otra síntesis de la lycopodina publicada por Kraus.¹⁸ En este trabajo, a partir de una enona y por adición de 3-oxobutanoato de etilo, hidrólisis del éster y descarboxilación se sintetiza el intermedio **XVI** (Esquema 3.4). A continuación se lleva a cabo una dihidroxilación del doble enlace, formación del sulfonato y sustitución del alcohol terciario por bromo. Finalmente este producto **XVII**, por reacción con 3-amino-1-propanol es transformado en el compuesto tricíclico **XVIII** a partir del cual se puede obtener la lycopodina siguiendo los últimos pasos de la síntesis de la lycopodina y licodolina de Heathcock (oxidación de Oppenauer, condensación aldólica e hidrogenación de la enona obtenida).



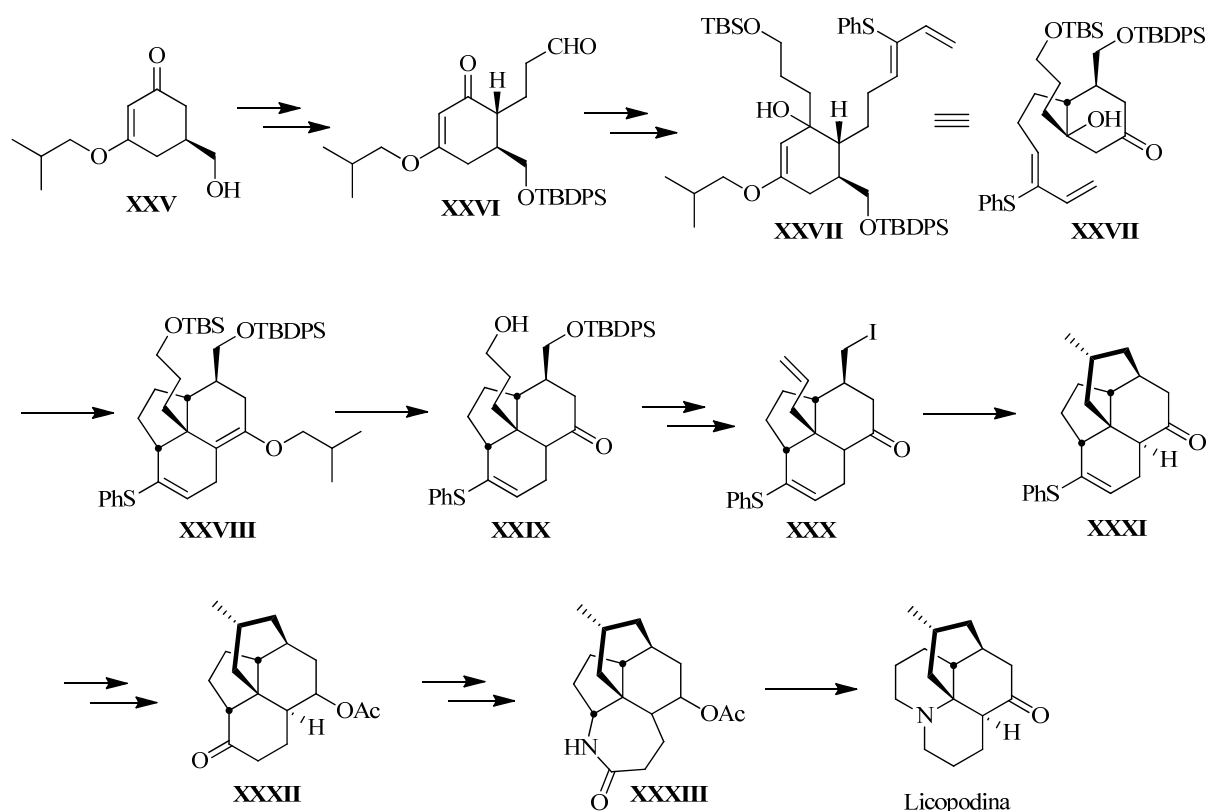
Esquema 3.4. Síntesis de la lycopodina de Kraus.¹⁸

Otra estrategia muy distinta es la presentada en 1997 por Padwa.²¹ Este grupo publicó una síntesis formal de la lycopodina a partir de la α -dialo imida **XIX** que por tratamiento con un catalizador de rodio da lugar a un 1,3-dipolo capaz de reaccionar con el doble enlace dando lugar a una mezcla de los intermedios **XX** y **XXI** (Esquema 3.5). A continuación este cicloadducto es tratado con un ácido de Lewis lo que provoca una apertura de anillo y la formación del intermedio **XXII** que sigue reaccionando mediante una ciclación π hasta llegar al compuesto **XXIII**. Finalmente se obtiene el producto **XXIV** que es un intermedio de la síntesis de la lycopodina de Stork mediante eliminación del grupo hidroxilo, hidrólisis del éster, descarboxilación, reducción de la lactama y desprotección de la amina.



Esquema 3.5. Síntesis formal de la lycopodina de Padwa.²¹

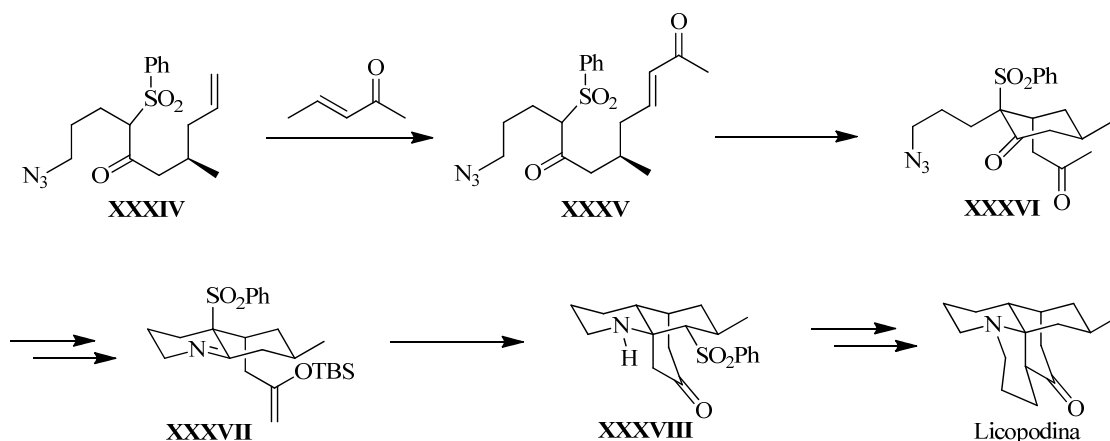
En 1998, Grieco publicó otra síntesis de la lycopodina.¹⁹ Partiendo de la enona **XXV** ya descrita se llega al intermedio **XXVI** mediante protección del alcohol primario y alquilación en α de la cetona (Esquema 3.6). Posteriormente se hace reaccionar al aldehído con un borano para formar un dieno y se lleva a cabo una adición sobre la cetona. Con este intermedio **XXVII** se lleva a cabo una reacción de Diels-Alder intramolecular que permite obtener el tricyclo **XXVIII**. A continuación de forma la hidroxiketona **XXIX** en medio ácido y a partir de ella el yoduro **XXX** con el cual se lleva a cabo una ciclación radicalica obteniéndose el cuarto anillo. Seguidamente se reduce la cetona protegiéndose el alcohol y se hidroliza el tioenol éter. El compuesto **XXXII** así obtenido es transformado en la amida **XXXIII** mediante formación de una oxima y transposición de Beckmann para finalmente obtener la lycopodina a través de una reducción, cloración de la amina, reoxidación del alcohol, transposición de Stieglitz y reducción de la imina.



Esquema 3.6. Síntesis de la lycopodina de Grieco.¹⁹

Por último en 2008, Carter publicó la primera síntesis enantioselectiva de este alcaloide.²⁰ La estrategia de este grupo se basa en una reacción de Michael intramolecular y diastereoselectiva a partir del intermedio lineal **XXXV** el cual es sintetizado mediante una reacción de metátesis de olefinas entre los alquenos **XXXIV** y la 3-penten-2-ona (Esquema 3.7). A continuación se reduce la azida a la correspondiente amina formándose la imina **XXXVI**. Tras la formación del silil enol éter correspondiente, se lleva a cabo la segunda etapa clave de la síntesis que es una reacción de Mannich intramolecular. De esta manera se obtiene el compuesto tricíclico **XXXVIII** en el que ha tenido lugar además una transposición del grupo sulfona. Por último se sintetiza la lycopodina mediante eliminación de la sulfona, alquilación de la amina con 3-yodo-1-propanol, oxidación de Oppenauer e hidrogenación del doble enlace de la enona.

En nuestro caso también centramos nuestra atención en este tipo de estructuras y dados los buenos resultados obtenidos en la síntesis de sistemas policíclicos nitrogenados mediante reacción en cascada presentados en el capítulo 2 de esta tesis, pensamos en la posibilidad de aplicar dicha metodología a la síntesis de la lycopodina.

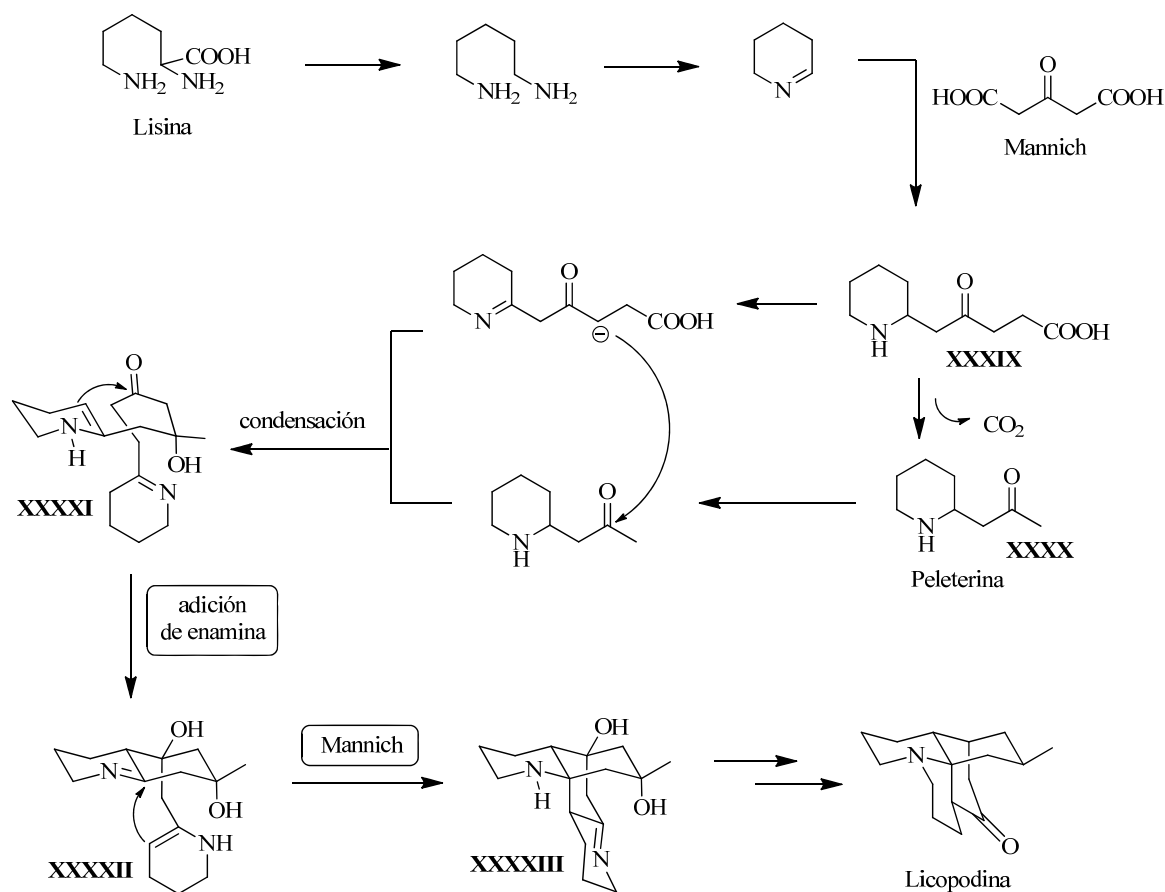
Esquema 3.7. Síntesis de la lycopodina de Carter.²⁰

3.2.- EXPOSICIÓN DE RESULTADOS.

3.2.1.- Estrategia planteada para la síntesis de la lycopodina.

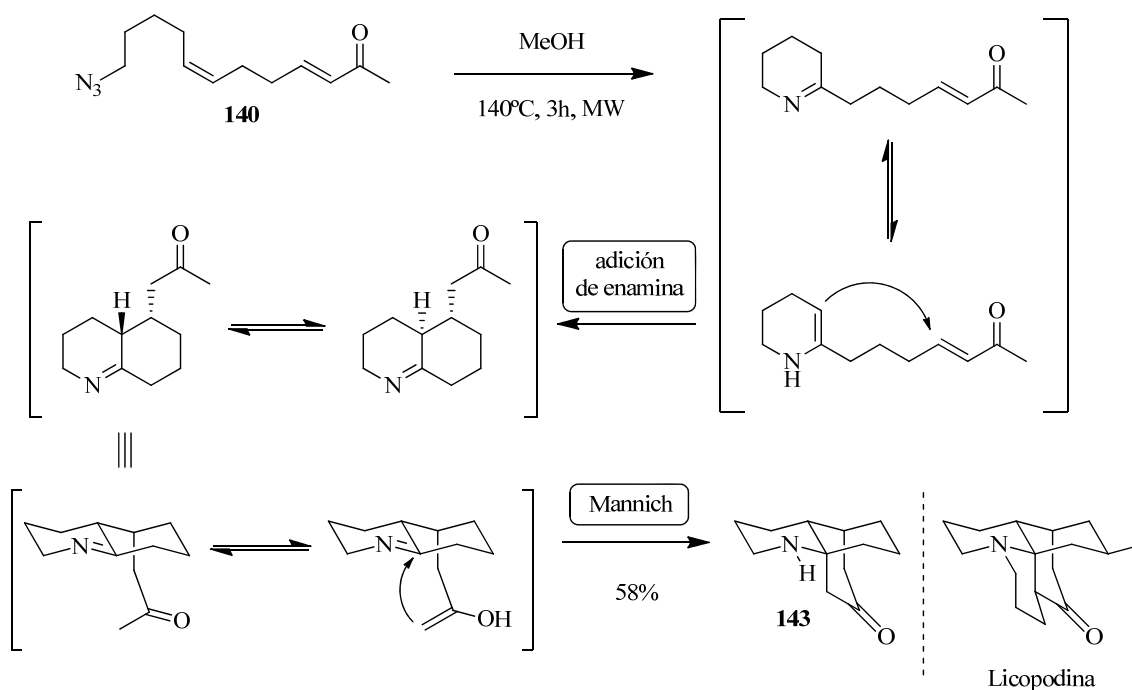
Nuestra estrategia para la síntesis de este alcaloide surgió a partir de su ruta biosintética, propuesta por el grupo de Spenser de la Universidad de McMaster (Esquema 3.8).²⁴ Mediante estudios de marcaje isotópico, demostraron que el esqueleto de la lycopodina se forma a partir de la condensación de una molécula de peleterina (XXXX) y otra derivada de ella con un ácido carboxílico (XXXIX), cada una de las cuales procede de una reacción de Mannich entre el ácido 3-oxo-pentanodioico y una molécula de piperideina, originada a partir de la lisina. La ruta prosigue con una adición de la enamina a la cetona formándose el esqueleto de la phlegmarina (XXXXI) a partir del cual se forma la lycopodina a través de una reacción de tipo Mannich entre una enamina y una imina seguida de una serie de oxidaciones y reducciones. Como etapas claves, por tanto, se pueden destacar la adición de una imina cíclica en su forma tautomérica de enamina sobre una cetona y una reacción de Mannich.

²⁴ a) R. N. Gupta, M. Castillo, D. B. MacLean, I. D. Spenser, J. T. Wrobel, *J. Am. Chem. Soc.* **1968**, *90*, 1360-1361; b) M. Castillo, R. N. Gupta, D. B. MacLean, I. D. Spenser, *Can. J. Chem.* **1970**, *48*, 1893-1903; c) M. Castillo, R. N. Gupta, Y. K. Ho, D. B. MacLean, I. D. Spenser, *Can. J. Chem.* **1970**, *48*, 2911-2918; d) M. Castillo, R. N. Gupta, Y. K. Ho, D. B. MacLean, I. D. Spenser, *J. Am. Chem. Soc.* **1970**, *92*, 1070-1075; e) J.-C. Braekman, R. N. Gupta, D. B. MacLean, I. D. Spenser, *Can. J. Chem.* **1972**, *50*, 2591-2602; f) W. D. Marchall, T. T. Nguyen, D. B. MacLean, I. D. Spenser, *Can. J. Chem.* **1975**, *53*, 41-50; g) T. Hemscheidt, I. D. Spenser, *J. Am. Chem. Soc.* **1993**, *115*, 3020-3021; h) T. Hemscheidt, I. D. Spenser, *J. Am. Chem. Soc.* **1996**, *118*, 1799-1800.



Esquema 3.8. Biosíntesis de la licopodina.

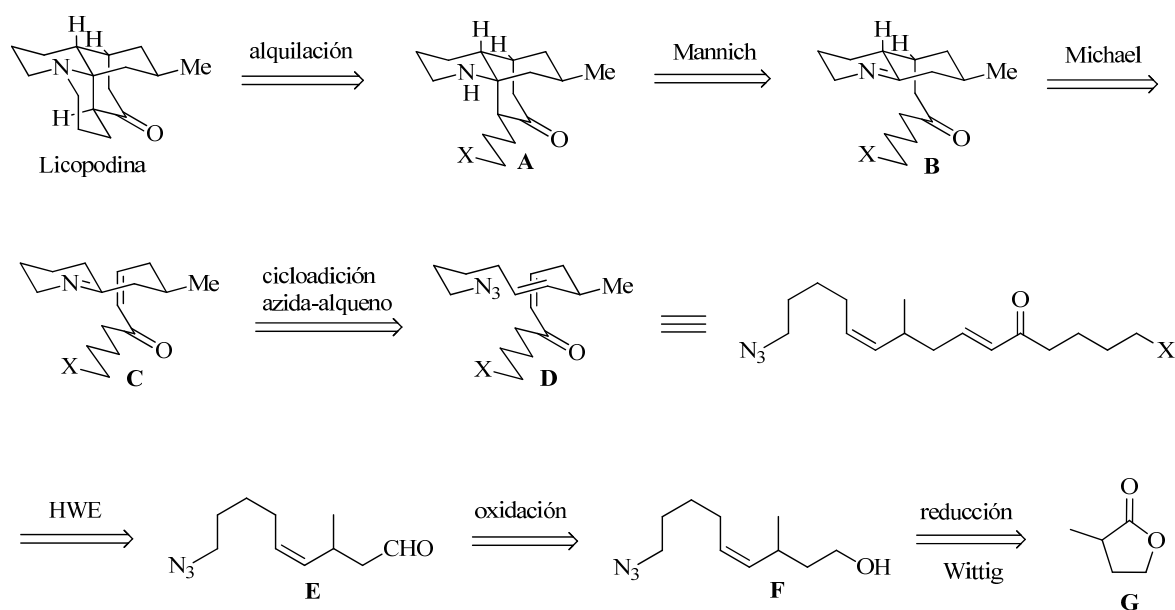
Esta ruta recuerda enormemente a la seguida en la formación del compuesto **143** a partir del azido alqueno **140** comentada en el capítulo anterior (Esquema 3.9). En este caso también el mecanismo está basado en la adición de una enamina sobre un electrófilo (una enona en este caso) y una reacción de Mannich intramolecular. Además puede comprobarse que el esqueleto de esta amina **143** se corresponde con tres de los anillos de la licopodina. Así pues, basados en estas premisas, pensamos que esta metodología podría ser muy útil para a síntesis de la licopodina y nos propusimos sintetizar este producto natural siguiendo el esquema retrosintético que se presenta a continuación (Esquema 3.10).

Esquema 3.9. Síntesis de la amina tricíclica **143**.

Pensamos que este alcaloide podría obtenerse por alquilación de la amina tricíclica **A** convenientemente funcionalizada. A su vez este intermedio sería el resultado de una reacción de Mannich intramolecular de la imina **B** fruto de una reacción de cicloadición 1,3-dipolar azida-alqueno intramolecular y posterior adición de Michael de la enamina endocíclica sobre el doble enlace deficiente en electrones. Por tanto, para la síntesis de la lycopodina se necesitaría preparar una enona lineal **D**.

Este precursor lineal es muy similar a los preparados en el capítulo anterior y por tanto su síntesis puede llevarse a cabo siguiendo la misma estrategia. Así el azido alqueno **D** podría sintetizarse a partir del aldehído **E** mediante la reacción con un fosfonato convenientemente funcionalizado a través de una reacción de Horner-Wadsworth-Emmons. Este aldehído sería obtenido a su vez, desde el correspondiente alcohol **F**, tras reducción de la lactona **G** y reacción del lactol resultante con la sal de fosfonio funcionalizada con el grupo azida empleando una reacción de Wittig como en ocasiones anteriores. Si bien es cierto que con este planteamiento se obtendría la lycopodina racémica, se trata de una síntesis muy corta y directa. Posteriormente, se podría obtener el producto ópticamente puro sin más que sintetizando el azido alqueno **D** enantioméricamente puro empleando, por ejemplo, las oxazolidinas quirales de Evans²⁵.

²⁵ D. A. Evans, A. E. Weber, *J. Am. Chem. Soc.* **1986**, 108, 6757-6761.



Esquema 3.10. Esquema retrosintético de la licopodina.

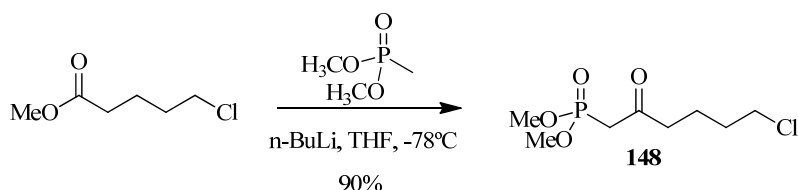
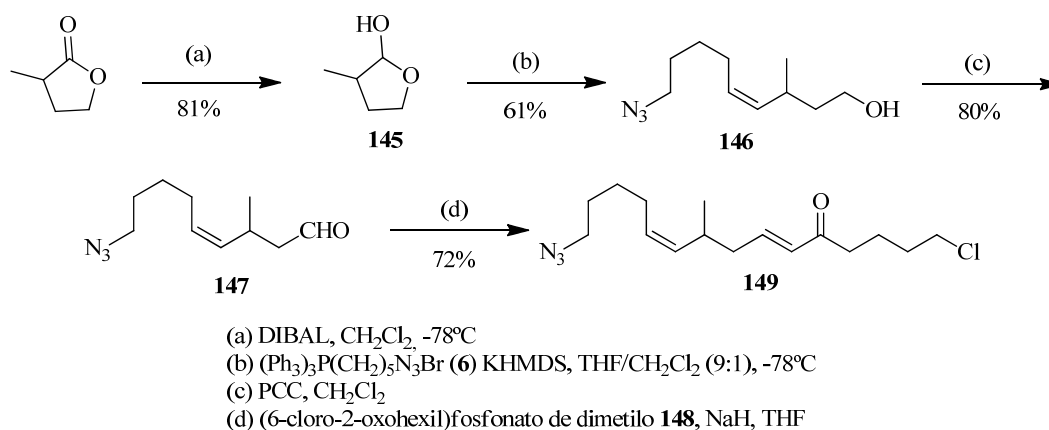
3.2.2.- Intentos de síntesis de la licopodina a partir del precursor lineal (6E,10Z)-15-azido-1-cloro-9-metilpentadeca-6,10-dien-5-ona.

En primer lugar se pensó en preparar el precursor lineal donde $\text{X} = \text{Cl}$. De esta manera al obtenerse la amina tras la reacción de Mannich, ésta podría ciclar espontáneamente mediante una reacción $\text{S}_{\text{N}}2$ para obtener directamente la licopodina. Así la reducción de la 3-metil- γ -butirolactona condujo al lactol **145**²⁶ que sin necesidad de ser purificado se hizo reaccionar con la sal de fosfonio **6** para dar lugar al alcohol **146** mediante una reacción de Wittig en las condiciones habituales de reacción (Esquema 3.11). La oxidación de dicho alcohol con PCC condujo con buen rendimiento al correspondiente aldehído **147**. Finalmente se empleó el fosfonato **148**, preparado a partir del éster 5-cloropentanoato de metilo,²⁷ para sintetizar el compuesto deseado **149** empleando una reacción de Horner-Wardsworth-Emmons.²⁸

²⁶ A. W. Schammel, B. W. Boal, L. Zu, T. Mesganaw, N. K. Garg, *Tetrahedron*, **2010**, 66, 4687-4695.

²⁷ N. A. Khatri, H. F. Schmitthener, J. Shringarpure, S. M. Weinreb, *J. Am. Chem. Soc.* **1981**, 103, 6387-6393.

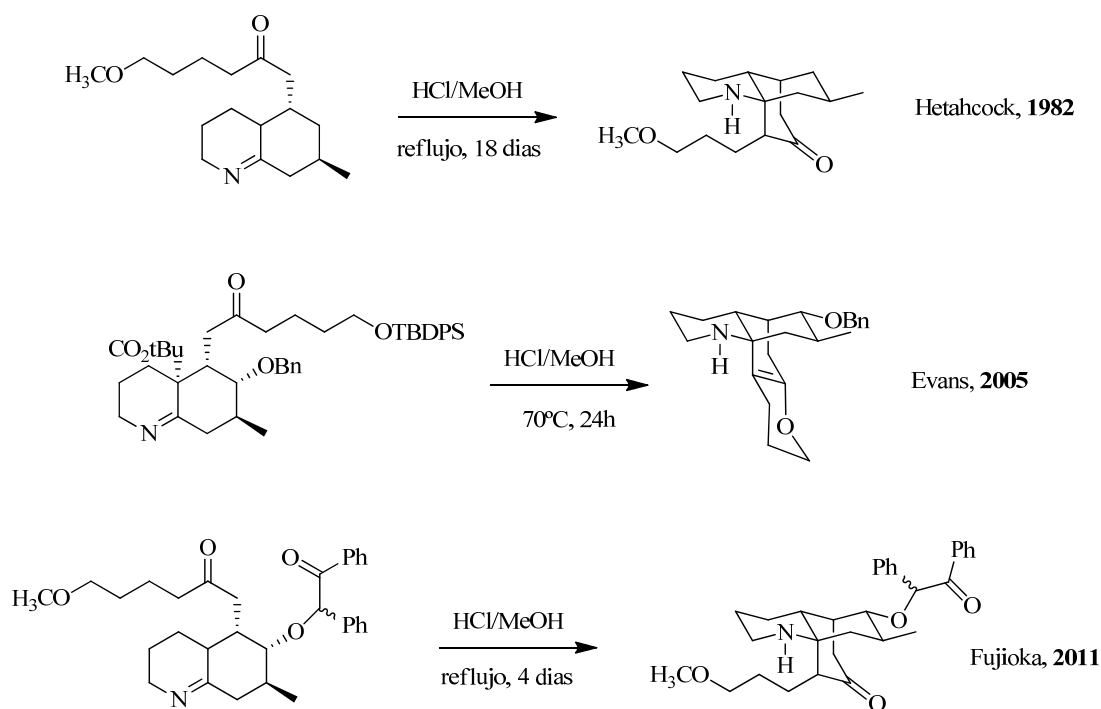
²⁸ K. J. Frankowski, B. Neuenswander, J. Aubé, *J. Comb. Chem.* **2008**, 10, 721-725.

Esquema 3.11. Síntesis del compuesto **149**.

A continuación se procedió a ensayar la reacción de ciclación en cascada con el objetivo de encontrar las mejores condiciones. En el capítulo 2 ya se comprobó como a partir de estas azido dienonas en metanol es posible obtener las correspondientes iminas bicíclicas, si bien la reacción de Mannich intramolecular únicamente se observó con la metil cetona. Por otro lado es conocido que dicha reacción de Mannich sí es posible con otras cetonas menos reactivas, al emplear HCl/MeOH tal y como describió Heathcock en su síntesis de la lycopodina.¹⁵ También los grupos de Evans²⁹ y Fujioka³⁰ emplean HCl/MeOH para llevar a cabo una reacción de Mannich con buenos resultados en sus respectivas síntesis de la clavolonina (8-hidroxilicopodina) (Esquema 3.12).

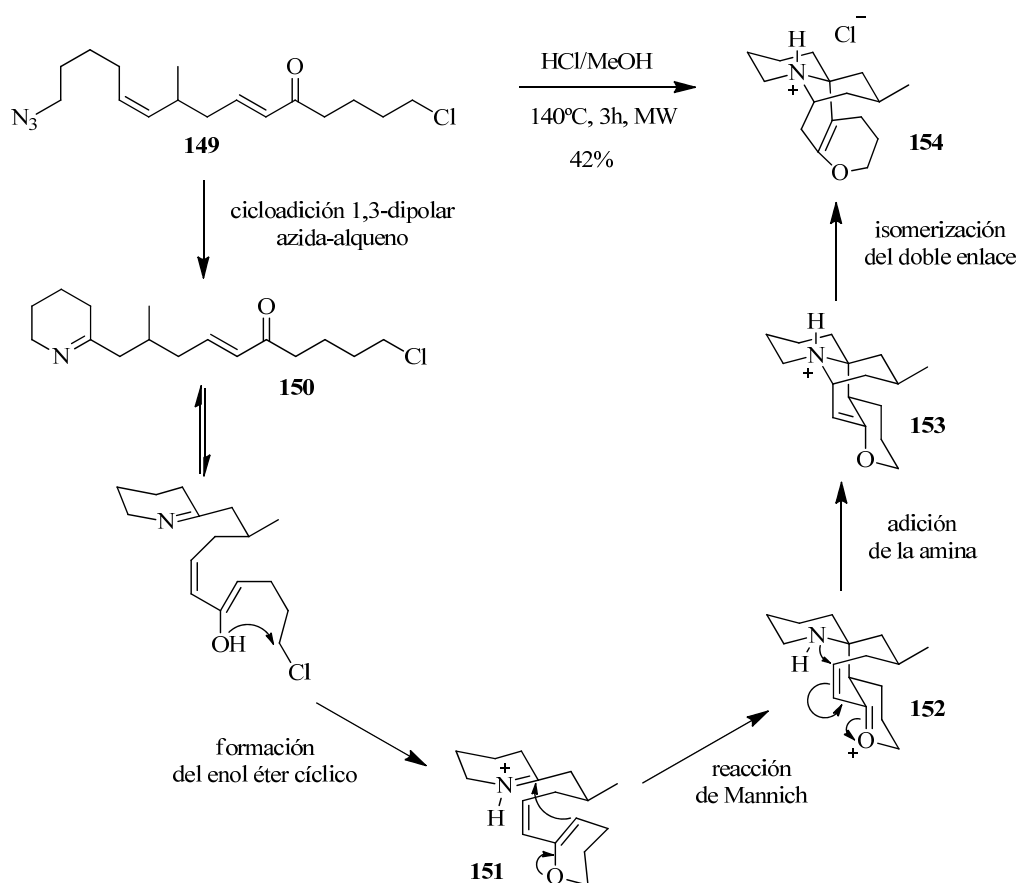
²⁹ D. A. Evans, J. R. Scheerer, *Angew. Chem. Int. Ed.* **2005**, *44*, 6038-6042.

³⁰ K. Nakahara, K. Hirano, R. Maehata, Y. Kita, H. Fujioka, *Org. Lett.* **2011**, *13*, 2015-2017.



De esta manera, con el objetivo de llevar a cabo la cicloadición 1,3-dipolar azida-alqueno, la adición de Michael y la reacción de Mannich en una sola etapa, se decidió calentar una disolución del azido alqueno **149** durante 3 horas a 140°C en el reactor microondas. Tras la purificación del crudo de reacción, se obtuvo con un 42% de rendimiento, un compuesto con una masa igual a la de la lycopodina, pero cuyo espectro de ¹H-RMN no se correspondía con el esperado. Tras una exhaustiva caracterización por resonancia magnética nuclear, espectrometría de masas e IR, se dilucidó su estructura y se comprobó que se trataba del enol éter tetracíclico **154** (Esquema 3.13). Dicha estructura pudo ser además confirmada mediante estudio de difracción de rayos X (Figura 3.2).³¹

³¹ Los datos de difracción de rayos X del compuesto **154** se encuentran en el anexo II. Dichos datos confirman que se trata del bromhidrato de esta amina tetracíclica, si bien lo esperado es la formación del clorhidrato. Actualmente se está investigando por medio de otras técnicas el origen de este átomo de bromo así como la posible coexistencia del clorhidrato y del bromhidrato en la muestra.



Esquema 3.13. Mecanismo de síntesis del tetracyclo **154**.

Posiblemente dicho producto se forma a través de un mecanismo por etapas comenzando con la cicloadición 1,3-dipolar azida-alqueno intramolecular que da lugar a la imina cíclica **150**, al mismo tiempo que se forma un enol éter cíclico mediante el ataque del enolato de la cetona sobre el cloro. El ácido clorhídrico protona la imina haciendo al carbono de la misma más electrófilo, y favoreciendo que tenga lugar una reacción de Mannich con el enol éter,³² en vez de la esperada adición de Michael de la enamina.³³ Posteriormente el nitrógeno de la amina resultante **152**, ataca al carbono electrófilo del doble enlace formándose el último anillo y obteniéndose el producto final tras la isomerización del doble enlace. Así pues, el problema radica en el orden de reacción, ya que el compuesto **151** reacciona a través de una reacción de Mannich, antes de darse la deseada adición de la enamina.

³² En su síntesis de la clavolonina Evans describe una reacción de Mannich muy similar entre un catión iminio y un enoléter como éste (D. A. Evans, J. R. Scheerer, *Angew. Chem. Int. Ed.* **2005**, *44*, 6038-6042.)

³³ Una reacción de Mannich similar es empleada también en la síntesis de la porantherina: D. M. Ryckman, R. V. Stevens, *J. Am. Chem. Soc.* **1987**, *109*, 4940-4948.

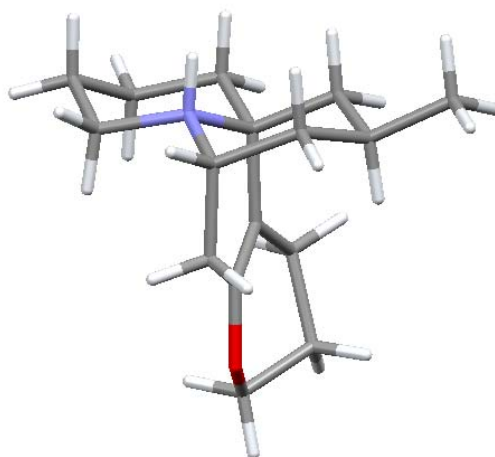


Figura 3.2. Estructura de difracción de rayos X del catión del compuesto **154**.

Se pensó entonces en emplear otros disolventes con el fin de encontrar alguno en el que el orden de reacción fuese el deseado (Tabla 3.1). En primer lugar se optó por el metanol y el resultado fue de nuevo la formación del enol éter **154** (entrada 1). Este resultado parece inesperado ya que anteriormente se vio que en metanol no tenía lugar la reacción de Mannich. Sin embargo en este caso el HCl liberado en la formación del anillo de dihidropirano protona la imina y la hace más reactiva frente a la reacción de Mannich, pudiendo tener lugar en este disolvente.

Se probaron también DMF y tolueno así como mezclas DMF/EtOH (4:1) y DMF/H₂O (4:1) como disolventes (entradas 2-5). Sin embargo, el resultado en los cuatro casos fue un crudo de reacción complejo, donde no se observó producto de partida tras 3 horas en el horno microondas a 140°C. Tampoco se identificaron las señales de ¹H-RMN características de enol éter **154**, ni se encontraron evidencias de la presencia de los protones en posición α a la imina, o a la amina en caso de que se hubiese dado la reacción de Mannich.

Se probó igualmente con un ácido de Lewis, el BF₃•Et₂O (entrada 6), pero de nuevo no se observaron los productos deseados, ni la amina tetracíclica **154**. El empleo de bases, tanto orgánicas (Et₃N) como inorgánicas (NaHCO₃ y K₂CO₃), tampoco condujo a un buen resultado y la identificación de los productos formados fue de nuevo imposible (entradas 7 a 9). Se realizaron otros dos ensayos utilizando KI (entradas 10 y 11). El resultado fue la formación del enol éter **154** ya que posiblemente tiene lugar una sustitución del cloro por el yodo que, al ser un mejor grupo saliente, favorece la formación del anillo de dihidropirano. Así cuando se empleó una mezcla DMF/EtOH (4:1) como disolvente y 1.8 equivalentes de KI se obtuvo el enol éter **154** con el mayor rendimiento siendo éste de un 57%.

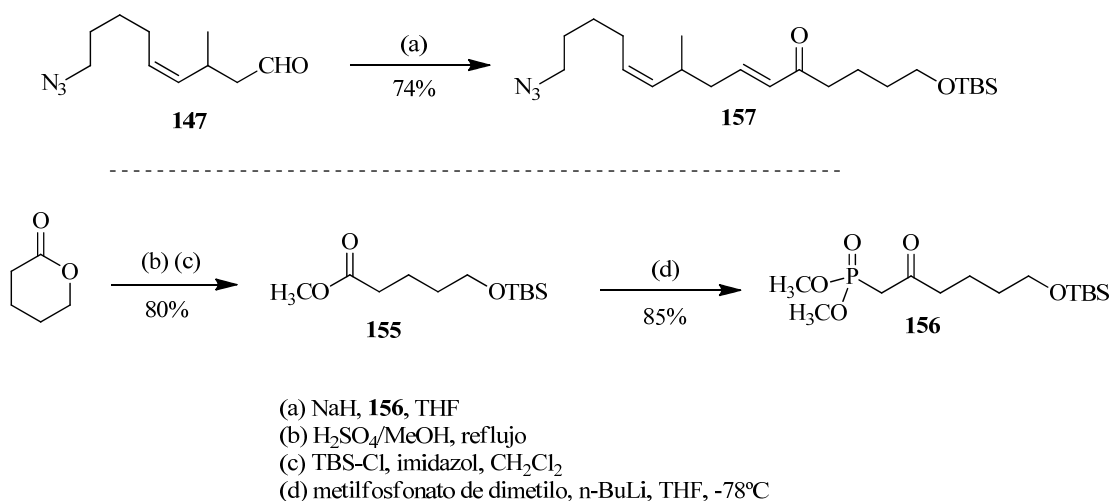
Tabla 3.1. Ciclación del precursor lineal de la lycopodina **149**.

Entrada	Disolvente	Ácido/Base	Aditivo	Producto (Rdto)
1	Metanol	-	-	Enol éter 154 (45%)
2	DMF	-	-	-
3	Tolueno	-	-	-
4	DMF/EtOH (4:1)	-	-	-
5	DMF/H ₂ O (4:1)	-	-	-
6	DMF/EtOH (4:1)	BF ₃ ·Et ₂ O	-	-
7	DMF	Et ₃ N	-	-
8	DMF/H ₂ O (4:1)	NaHCO ₃	-	-
9	DMF/H ₂ O (4:1)	K ₂ CO ₃	-	-
10	DMF	-	KI	Enol éter 154 (42%)
11	DMF/EtOH	-	KI	Enol éter 154 (57%)

3.2.3.- Intentos de síntesis de la lycopodina a partir del precursor lineal (6E,10Z)-15-azido-1-[(*tert*-butildimetilsilil)oxi]-9-metilpentadeca-6,10-dien-5-ona.

Dados los malos resultados obtenidos con esta azido dienona se pensó en emplear otro grupo funcional en el extremo de la cadena, en vez del cloro. Se optó por un grupo hidroxilo protegido como TBS, producto que se obtuvo por reacción del aldehído **147** con el fosfonato **156** (Esquema 3.14). A su vez este fosfonato se preparó desde la δ -valerolactona por reacción con H₂SO₄ en metanol y posterior protección del alcohol con cloruro de *tert*-butildimetilsililo (TBS-Cl) para obtener el éster **155**³⁴ y reacción del mismo con metilfosfonato de dimetilo empleando n-BuLi como base.

³⁴ M. Brewer, C. A. James, D. H. Rich, *Org. Lett.* **2004**, 6, 4779-4782.

**Esquema 3.14.** Síntesis del compuesto **157**.

Para la ciclación de **157** también se probaron varias condiciones de reacción (Tabla 3.2). Así, por ejemplo al emplear MeOH (entrada 1) se obtuvo la esperada imina bicíclica **158** tal y como se observó en el crudo de reacción³⁵ (Esquema 3.15). Sin embargo, ésta resultó inestable y no pudo aislarse para su caracterización. Se intentó entonces llevar a cabo directamente la reacción de Mannich calentando el crudo en HCl/MeOH, pero ésta no tuvo lugar y el producto se descompuso.

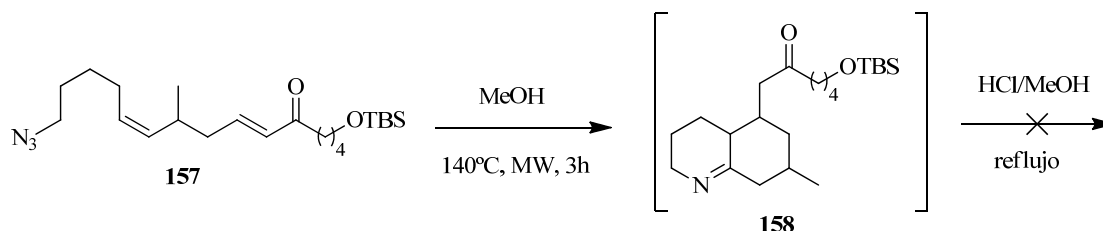
Tabla 3.2. Ciclación del precursor lineal de la lycopodina **157**.

Entrada	Disolvente	Resultado
1	Metanol	Imina 158
2	DMF	-
3	Tolueno	-
4	DMF/EtOH (4:1)	-
5	HCl/MeOH	Enol éter 154

Se probó también con HCl/MeOH como disolvente para llevar a cabo la reacción bajo radiación por microondas (entrada 5), pero se obtuvo el enol éter tetracíclico **154** ya que en medio ácido el grupo protector del alcohol es eliminado y se forma de nuevo el anillo de dihidropirano con el que tiene lugar la

³⁵ En el ¹H-RMN se observaron las señales características de los protones en α de la imina.

reacción de Mannich favorecida en medio ácido (Esquema 3.13). Igualmente se probaron otros disolventes como tolueno, DMF o DMF/EtOH (4:1) (entradas 2, 3 y 4). Sin embargo, no se obtuvieron mejores resultados y como ocurrió con la azido dienona funcionalizada con el cloro, el resultado fue un crudo de reacción complejo del que no se pudieron identificar los productos formados.



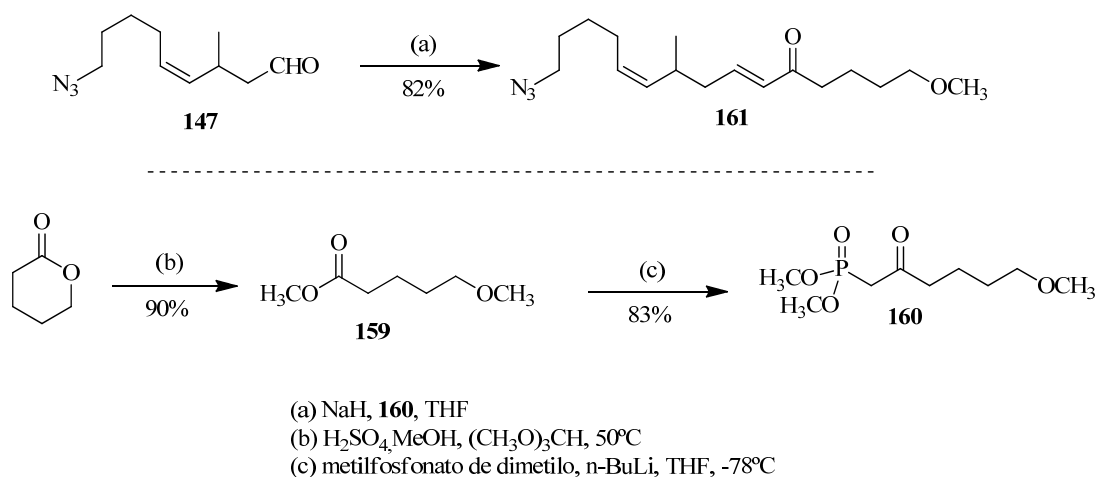
Esquema 3.15. Ciclación de la azido dienona **157**.

3.2.4.- Intentos de síntesis de la lycopodina a partir del precursor lineal (6*E*,10*Z*)-15-azido-9-metil-1-metoxipentadeca-6,10-dien-5-ona.

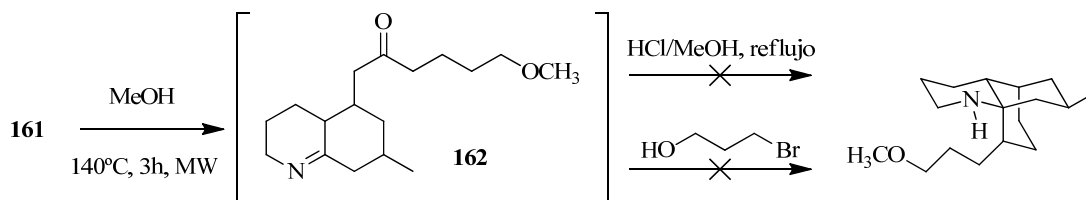
Se pensó entonces en emplear el compuesto funcionalizado con un grupo metoxilo ya que éste es empleado con éxito en la síntesis de la lycopodina de Heathcock¹⁵ y en las síntesis de la clavolonina de Fujioka³⁰ y Breit.³⁶ Para preparar este precursor fue necesario primero preparar el fosfonato **160** empleando un método desarrollado por King para la síntesis de alcoxi ésteres a partir de lactonas (Esquema 3.16).³⁷ Así la reacción de la δ -valerolactona con trimetilortoacetato en MeOH y H₂SO₄ permitió obtener directamente el 5-metoxipentanoato de metilo con muy buen rendimiento. Posteriormente se empleó metilfosfonato de dimetilo con n-BuLi para obtener el deseado fosfonato. Por último, la reacción de este fosfonato con el aldehído **147** condujo a la enona **161**.

³⁶ K. M. Laemmerhold, B. Breit, *Angew. Chem. Int. Ed.* **2010**, *49*, 1-5.

³⁷ S. A. King, *J. Org. Chem.* **1994**, *59*, 2253-2256.

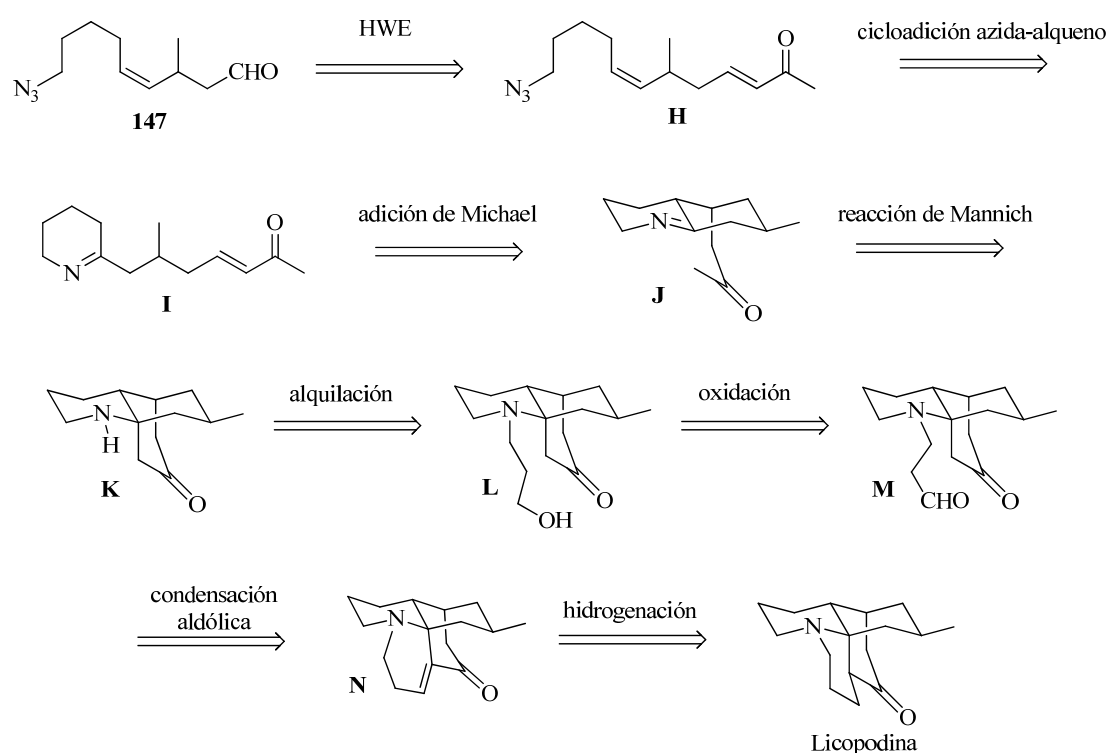
**Esquema 3.16.** Síntesis del compuesto **161**.

En este caso se probó también la ciclación en metanol y tras 3 horas a 140°C en el horno microondas se observaron evidencias de la formación de la imina bicíclica **162** en el crudo de reacción, aunque ésta resultó imposible de purificar debido a su gran tendencia a la oxidación como ocurre con este tipo de iminas (Esquema 3.17). Se optó entonces por llevar a cabo la reacción de Mannich directamente, con el objeto de poder aislar y purificar la amina resultante que no debería ser inestable. Para ello se hizo reaccionar la imina con HCl/MeOH a reflujo, reacción que llevó a cabo Heathcock en su síntesis de la lycopodina y que a pesar de necesitar un tiempo de reacción muy largo (18 días) le permitió obtener la correspondiente amina a través de una reacción de Mannich intramolecular. Sin embargo en nuestro caso, tras varios días de reacción no se observó cambio y se recuperó el producto de partida inalterado. Se intentó llevar a cabo también dicha reacción empleando 3-bromo-1-propanol, reactivo capaz de generar HBr en el medio y que fue empleado para llevar a cabo una reacción de Mannich similar en la síntesis de la clavolonina de Breit.³⁶ Desafortunadamente no se observó que tuviese lugar la formación de la amina tampoco de esta manera.

**Esquema 3.17.** Ciclación del compuesto **161**.

3.2.5.- Intentos de síntesis de la lycopodina a partir del precursor lineal (3E,7Z)-12-azido-6-metildodeca-3,7-dien-2-ona.

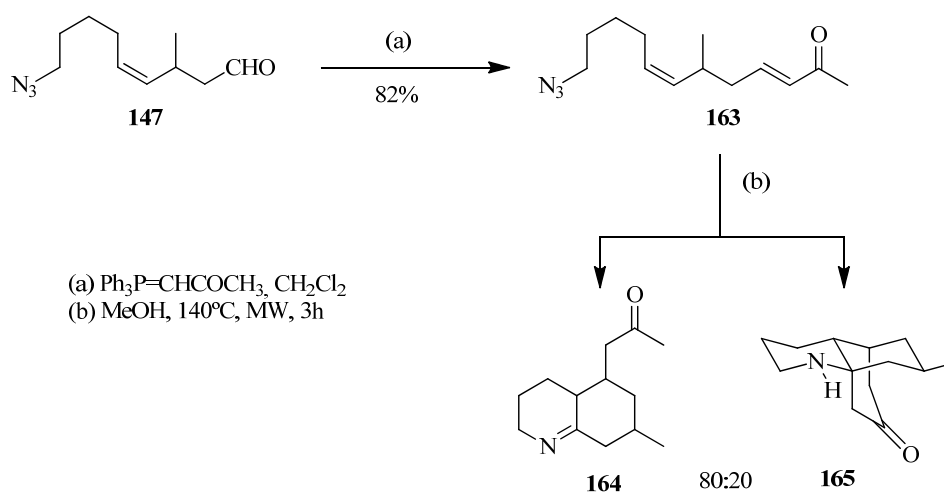
Llegados a este punto decidimos replantear la estrategia de síntesis, dada la imposibilidad de llevar a cabo la reacción de Mannich con estos sustratos. Así pues, teniendo en cuenta que sí habíamos observado una reacción de Mannich con una metil cetona en la síntesis de la amina tricíclica **143** (Esquema 3.9), pensamos en la posibilidad de llevar a cabo la misma reacción en cascada con la correspondiente metil cetona **H** con un grupo metilo en posición 6 (Esquema 3.18). De este modo se podría obtener el triciclo **K**, mediante una reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición de Michael/reacción de Mannich. A partir de aquí la síntesis de la lycopodina sería posible mediante la estrategia publicada por Heathcock en su síntesis de la licodolina¹⁵ y que posteriormente ha sido empleada también con éxito por Krauss¹⁸ y Carter²⁰ para sintetizar la lycopodina y por Snider para la obtención de la 7-hidroxilycopodina.³⁸ Dicha estrategia consiste en la alquilación de la amina con 3-yodo-1-propanol para obtener el alcohol **L**, posterior oxidación y condensación aldólica para obtener la enona **N**, y finalmente una hidrogenación catalítica para obtener la lycopodina.



Esquema 3.18. Estrategia planteada para la síntesis de la lycopodina.

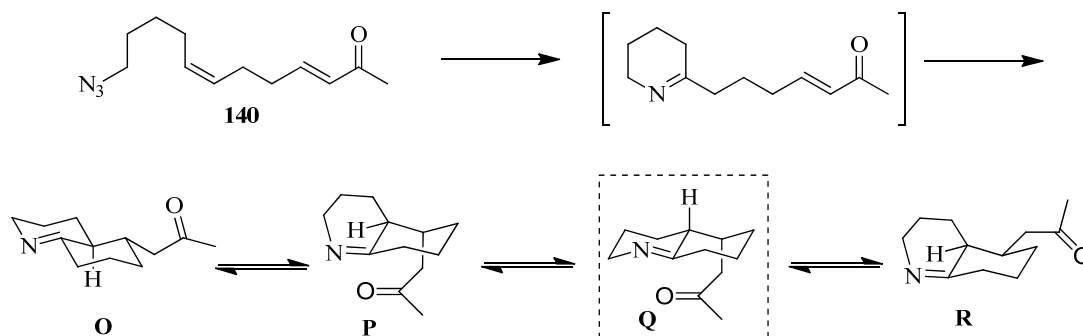
³⁸ a) H.-Y. Lin, B. B. Snider, *Org. Lett.* **2011**, *13*, 1234-1237; b) H.-Y. Lin, R. Causey, G. E. García, B. B. Snider, *J. Org. Chem.* **2012**, *77*, 7143-7156.

Así pues, se procedió a sintetizar la azido enona **163** a partir del aldehído **147** mediante una reacción de Horner-Wadsworth-Emmons que transcurrió con buen rendimiento (Esquema 3.19). A continuación se llevó a cabo la reacción de ciclación en cascada calentando en MeOH a 140°C en un reactor microondas. Sin embargo, a diferencia de lo que ocurría con la azido enona sin el grupo metilo, tras 3 horas de reacción únicamente se observó la formación de una pequeña cantidad de la amina **165**, siendo el producto mayoritario la imina **164**, aproximadamente en una proporción 80:20. Considerando que tal vez la reacción era más lenta en este caso, se aumentó el tiempo de reacción a 8 horas, pero no se pudo obtener una mayor cantidad de amina. Tampoco el calentamiento de esta mezcla en HCl/MeOH a 80°C durante varios días produjo un cambio en la proporción de los productos obtenidos.



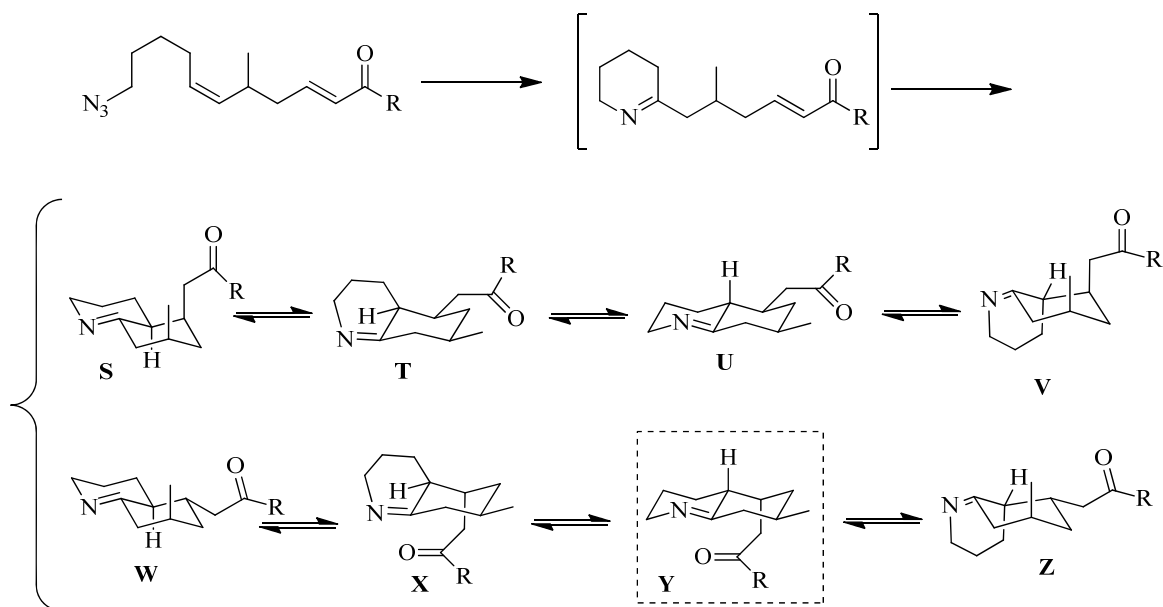
Esquema 3.19. Síntesis y ciclación de la azido dienona **163**.

Se pensó entonces que tal vez el problema era la estereoquímica de la imina bicíclica formada. En el caso de la azido dienona **140**, la reacción de adición de Michael puede dar lugar a cuatro iminas bicíclicas en equilibrio (Esquema 3.20). Las iminas **O** y **P** están en equilibrio conformacional ya que se trata de la misma imina, pero en la conformación silla-silla o bote-silla, lo mismo sucede con las iminas **Q** y **R**. Por otro lado las estructuras **O** y **P** pueden interconvertirse en las **Q** y **R** a través de la epimerización en el carbono 4a. Por tanto las cuatro iminas se encuentran en equilibrio y a pesar de que únicamente la **Q** es capaz de evolucionar a través de una reacción de Mannich, al final puede haber una conversión total.



Esquema 3.20. Posibles iminas formadas a partir de la azido dienona **140**.

Por el contrario las azido dienonas de partida sintetizadas con un grupo metilo a partir de la 3-metil- γ -butirolactona, contienen un centro estereogénico lo que se traduce en la posible formación de ocho iminas bicyclicas, según la configuración de los carbonos 4a, 5 y 7 del anillo de octahidroquinolina, y la conformación adoptada (Esquema 3.21). Estas iminas están en equilibrio cuatro a cuatro, pero no son todas interconvertibles. Por un lado las iminas **S** y **T** son dos conformeros del mismo compuesto (silla-silla y bote-silla respectivamente) y están en equilibrio a través de la epimerización en el carbono 4a con las iminas **U** y **V** (dos conformeros de la misma imina). La misma relación existe entre las estructuras **W**, **X**, **Y** y **Z**, pero estas cuatro iminas no están en equilibrio con las anteriores.

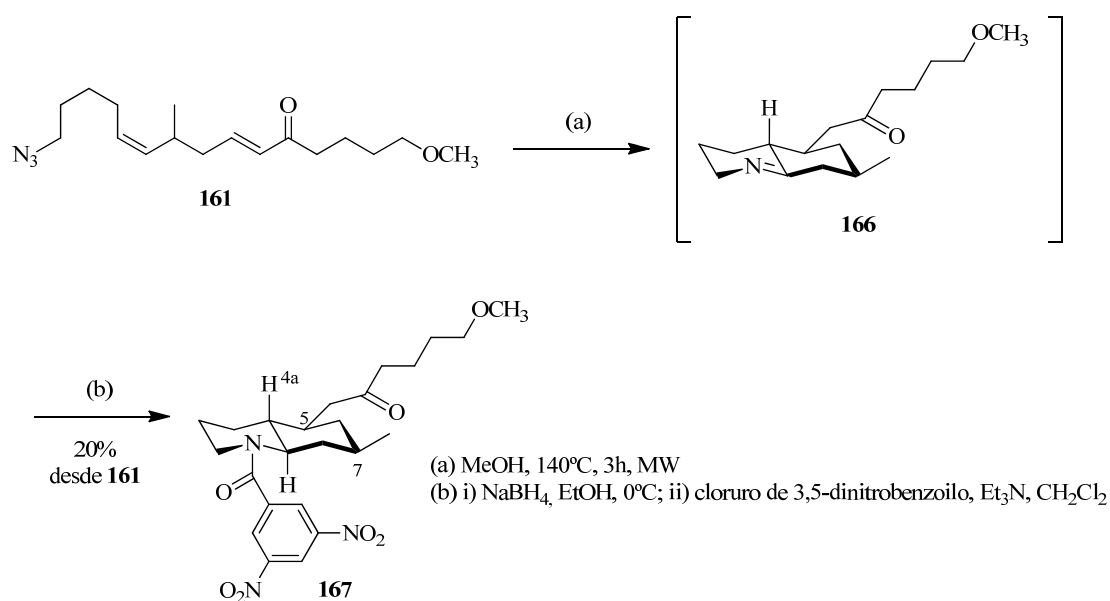


Esquema 3.21. Posibles iminas formadas en la reacción de adición de Michael.

De todas estas estructuras únicamente la **Y** es capaz de reaccionar a través de una reacción de Mannich. Como consecuencia, si durante la reacción de Michael se forman mayoritariamente las iminas **S**, **T**, **U** y **V**, éstas no pueden seguir reaccionando y se explicaría el hecho de que se observe una alta proporción de imina que no es capaz de dar la reacción de Mannich bajo ninguna condición. De hecho tan sólo se ha observado que tiene lugar la reacción de Mannich cuando $R = CH_3$, ya que con sustituyentes mayores probablemente la formación de las iminas **W**, **X**, **Y** y **Z** sea muy minoritaria.

Debido a la imposibilidad de purificar las iminas bicyclicas para estudiar su estereoquímica, se decidió ciclar de nuevo uno de los precursores lineales y proceder a la reducción directa del crudo con $NaBH_4$ para acilar seguidamente la amina obtenida y acceder así a la correspondiente amida que sí puede aislarse (Esquema 3.22). De ese modo se sintetizó la amida **167** la cual se obtuvo como un solo diastereoisómero, a partir del compuesto **161**. La configuración relativa de este producto se dedujo en base a su espectro NOESY y como puede verse el protón 4a se encuentra en posición axial, mientras que los sustituyentes en las posiciones 5 y 7 se encuentran en disposición ecuatorial adoptando una conformación que no puede dar la lycopodina (estructura tipo **T**, Esquema 3.21).

Como se ha comentado no se detectó otro isómero de esta amida **167** en el crudo de reacción lo cual indica que en la adición de Michael se forma de manera muy mayoritaria la imina de configuración no deseada que impide la posterior reacción de Mannich. Únicamente con la metil cetona **163** se observó una pequeña cantidad de producto Mannich probablemente porque al ser un sustituyente menos voluminoso pueda formarse un poco de imina con la cadena carbonada de la posición 5 en axial.



Esquema 3.22. Formación de la amida **167**.

Para estimar la energía relativa de cada una de las ocho iminas resultantes de la adición de Michael (dos conformeros, silla-silla y bote-silla, de cada uno de los cuatro diastereoisómeros, los cuales son dos parejas epiméricas en la posición C-4a), se ha empleado la molécula modelo **AA**³⁹ (Figura 3.3) y se han realizado modelizaciones computacionales.⁴⁰

Para el cálculo de la energía de las ocho iminas posibles se empleó como estructura de partida una decahidroquinolina sustituida en las posiciones 5 y 7, dada la ausencia de una estructura con una imina en la base cristalográfica. Sobre esta estructura se eliminó el átomo de hidrógeno unido al nitrógeno formándose a continuación el doble enlace, y se modificaron los sustituyentes para crear dos grupos metilo.

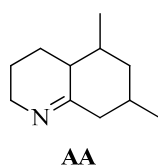


Figura 3.3. Estructura modelo empleada para los cálculos.

A partir de esta estructura se pudieron calcular las energías de los compuestos **U'** e **Y'** ya que la silla del carbociclo y la posición del protón 4a (axial) es la misma que la de la estructura de partida (Figura 3.4). Para calcular la energía de las estructuras **T'** y **X'** se modificó la posición del protón 4a a una posición ecuatorial. Sin embargo las otras cuatro estructuras (**S'**, **V'**, **W'** y **Z'**) tienen la silla del carbociclo invertida por lo que esta estructura ya no se corresponde con la de partida de la base cristalográfica y obliga a romper y formar los enlaces de nuevo para crear esta nueva silla. Esto no es posible con el programa Gaussian y se optó por calcular la energía de los enantiómeros de estas estructuras ya que es la misma y en este caso sí la forma de la silla es la de partida y no es necesario invertirla. Por tanto se calcularon las energías de las estructuras (**U'**, **Y'**, **T'**, **X'**, **ent-S'**, **ent-V'**, **ent-W'** y **ent-Z'**).

³⁹ Se ha usado un grupo metilo como sustituyente en la posición 5 en vez del grupo real para simplificar el cálculo. Se conservará la misma nomenclatura que para las iminas del esquema 3.20, pero nombradas con una prima (').

⁴⁰ Los cálculos se realizaron usando el método híbrido HF-DFT con el funcional B3LYP y la base 6-31G*, en el programa Gaussian.

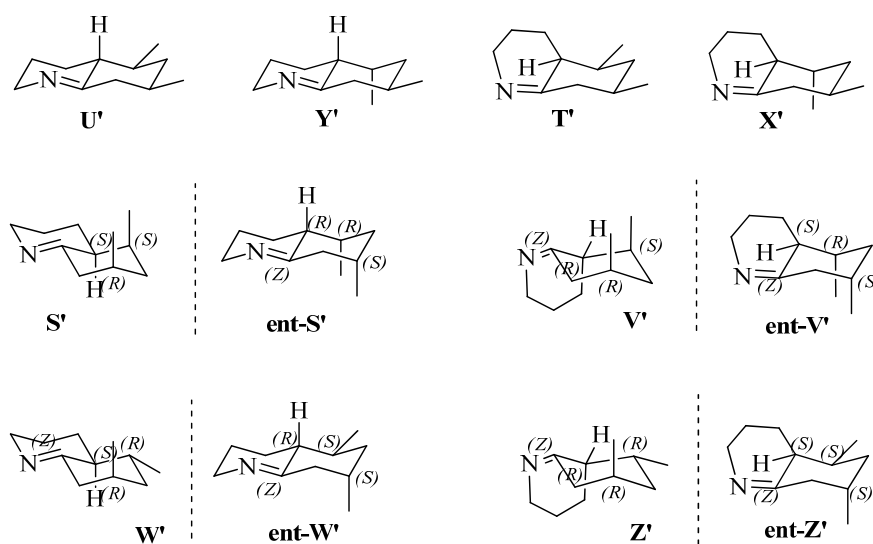


Figura 3.4. Estructuras modelizadas.

En la siguiente tabla (Tabla 3.3) pueden verse los resultados obtenidos. En ella se representan las iminas ordenadas de mayor a menor estabilidad con sus estructuras minimizadas, su energía electrónica (E) y energía libre relativa⁴¹ (ΔG), y la proporción de cada una de ellas calculada a partir de la ecuación de distribución de Boltzmann (Ecuación 3.1).

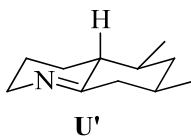
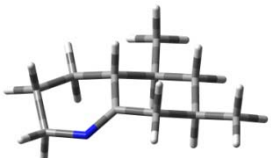
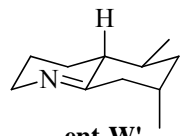

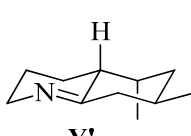
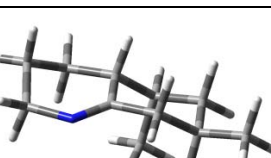
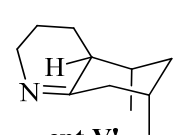
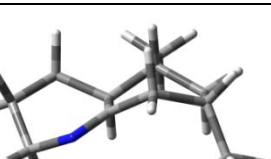
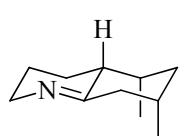
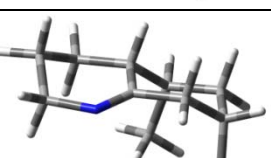
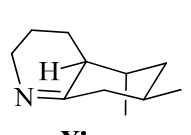
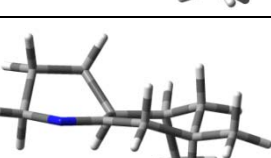
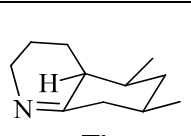
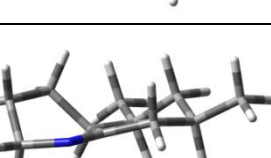
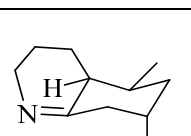
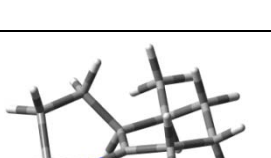
$$n_i = \frac{e^{-\frac{\Delta G_i}{K_B \cdot T}}}{\sum_i e^{-\frac{\Delta G_i}{K_B \cdot T}}}$$

Ecuación 3.1. Ecuación de distribución de Boltzmann.

A la vista de los datos obtenidos puede comprobarse que las estructuras con el protón 4a en posición axial, estructuras silla-silla, son más estables que las que tienen este protón en ecuatorial, estructuras bote-silla. Si bien es cierto que la imina **V'** tiene una conformación bote-silla y aparece en la tabla antes que la estructura **S'**, que es silla-silla, ambas tienen una energía muy parecida, cuya diferencia entra dentro del error del cálculo (0,05 kcal/mol). Además en la tabla las estructuras aparecen ordenadas según su energía libre, pero si se tiene en cuenta la energía electrónica, **S'** es más estable que **V'**.

⁴¹ Se asignó un valor 0 de energía a la estructura más estable.

Tabla 3.3. Datos obtenidos en la modelización de las estructuras.

Entrada	Compuesto	Estructura minimizada	Energías	Proporción
1	 U'		$\Delta G = 0$ kcal/mol $E = -485.375616$ u.a.	0,86
2	 ent-W'		$\Delta G = 1,80$ kcal/mol $E = -485.373006$ u.a.	0,097
3	 Y'		$\Delta G = 2,57$ kcal/mol $E = -485.371840$ u.a.	0,038
4	 ent-V'		$\Delta G = 6,81$ kcal/mol $E = -485.363900$ u.a.	$2,1 \cdot 10^{-4}$
5	 ent-S'		$\Delta G = 6,86$ kcal/mol $E = -485.365550$ u.a.	$2,2 \cdot 10^{-4}$
6	 X'		$\Delta G = 8,28$ kcal/mol $E = -485.361691$ u.a.	$3,7 \cdot 10^{-5}$
7	 T'		$\Delta G = 8,83$ kcal/mol $E = -485.361274$ u.a.	$1,9 \cdot 10^{-5}$
8	 ent-Z'		$\Delta G = 11,21$ kcal/mol $E = -485.357955$ u.a.	$1,0 \cdot 10^{-6}$

En cuanto a las proporciones de cada estructura la mayoritaria es la **U'**, con una proporción teórica de 0,86 (86%). Esto concuerda con el dato experimental ya que esta es la imina mayoritaria observada tal y como se vio al estudiar la estereoquímica de la amida **167** (Esquema 3.22). Seguidamente se encuentran las estructuras **W'** e **Y'** con unas proporciones de 0,097 (9,7%) y 0,038 (3,8%) respectivamente. A partir de ahí, las siguientes estructuras son ya muy minoritarias y pueden despreciarse. Así pues, la proporción final de imina/amina se puede obtener dividiendo la proporción de **U'** (producto que no da la reacción de Mannich), por la suma de las proporciones de **W'** e **Y'** (que sí pueden dar lugar al producto Mannich). El resultado es $0,86/(0,097 + 0,038) = 6,4$, lo cual está en concordancia con el dato experimental obtenido del espectro de ^1H -RMN del crudo de la reacción de ciclación de la azido dinenona **163**, donde se observaba una relación aproximada de imina/amina de 4 (80/20).

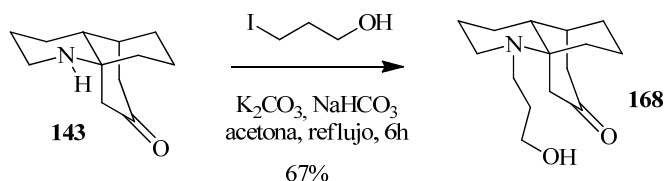
Parece por tanto, que los cálculos confirman que en la reacción de Michael se forma mayoritariamente la imina con los sustituyentes en posiciones 5 y 7 en ecuatorial, la cual no puede nunca adoptar la conformación adecuada para que tenga lugar la reacción de Mannich. Esto hace imposible obtener la licopodina con esta estrategia de síntesis.

Por otro lado, hay que destacar que, por lo que conocemos, esta es la primera vez que se describen cálculos *ab initio* de octahidroquinolinas sustituidas en posiciones 5 y 7, y nuestros resultados confirman que el método usado (B3LYP/6-31G*) es adecuado para modelizar este tipo de moléculas.

3.2.6.- Síntesis de la 15-desmetil licopodina.

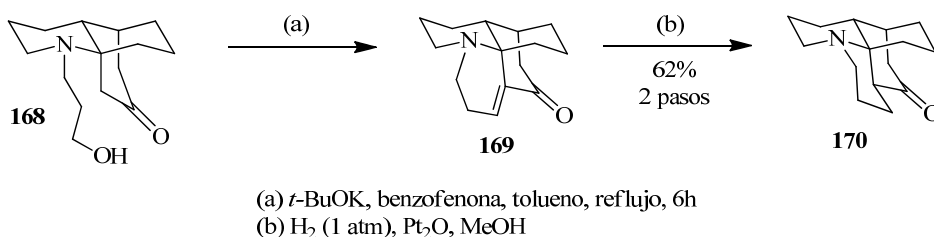
Dada por tanto la imposibilidad de sintetizar la licopodina por esta ruta nos planteamos la posibilidad de preparar la 15-desmetil licopodina ya, que como se comprobó en el capítulo 2, sin la presencia del metilo en la posición 9 sí puede tener lugar la reacción de Mannich con la metil cetona. De este modo y a través de una triple reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/reacción de Michael/reacción de Mannich del compuesto **140** se pudo obtener la amina tricíclica **143** (Esquema 3.9). Decidimos por tanto completar la síntesis de la 15-desmetil licopodina a partir de este intermedio del mismo modo que pensábamos obtener el producto natural; mediante alquilación con 3-yodo-1-propanol, oxidación y condensación aldólica y finalmente hidrogenación de la enona (Esquema 3.18).

Para proceder por tanto en primer lugar a la alquilación de la amina se hizo reaccionar el producto **143** con 3-yodo-1-propanol en presencia de K_2CO_3 y $NaHCO_3$ en acetona a reflujo durante 6 horas. De este modo se obtuvo el alcohol **168** (Esquema 3.23).



Esquema 3.23. Síntesis del alcohol **168**.

A continuación se llevó a cabo una oxidación de Oppenauer bajo las condiciones descritas por Woodward⁴² empleando *tert*-butoxido potásico y benzofenona en tolueno a reflujo (Esquema 3.24). Tal y como aparece descrito en la bibliografía el producto esperado de esta reacción es la enona **169** ya que bajo estas condiciones de reacción tiene lugar inmediatamente la condensación aldólica una vez oxidado el alcohol. Hay que destacar en este punto que este procedimiento es muy sensible a las condiciones de reacción. Por ello es muy importante para obtener un buen resultado emplear tolueno seco y desgasificado, además de mantener una atmósfera inerte en todo momento. Con estas precauciones se pudo obtener con éxito la esperada enona **169** que, sin necesidad de ser purificada, se sometió a una hidrogenación catalítica a presión atmosférica empleando como catalizador Pt_2O obteniéndose así finalmente la 15-desmetil licopodina (**170**) con un rendimiento global para las dos etapas del 62%.



Esquema 3.24. Síntesis de la 15-desmetil licopodina.

⁴² R. B. Woodward, N. L. Wendler, F. J. Brutschy, *J. Am. Chem. Soc.* **1945**, 67, 1425-1429.

PARTE EXPERIMENTAL

3.3.- PARTE EXPERIMENTAL.

A continuación se presenta la parte experimental correspondiente al capítulo de aproximación a la síntesis de alcaloides de *Lycopodium*. Tanto los procedimientos como la caracterización de los productos están redactados en inglés. Todas las reacciones con reactivos sensibles se realizaron en atmósfera inerte (argón) y con disolventes secos. La mayoría de los reactivos utilizados se adquirieron en Aldrich o Fluka y se usaron sin purificar.

3.3.1.- Técnicas generales utilizadas.

Cromatografía

Las cromatografías en capa fina (CCF) se realizaron empleando placas de gel de sílice (Merck, 60 F_{4/254}) de 0,2 mm de espesor, visualizándose las manchas con luz UV (365 nm y 254 nm) o mediante reveladores químicos como ácido fosfomolibdico, permanganato potásico o ninhidrina.

Las cromatografías en columna se realizaron con gel de sílice (Merck, 230-240 mesh ASTM) utilizando la técnica de columna seca con elución a presión (Flash chromatography).¹ El eluyente empleado es indicado en cada caso.

Resonancia magnética nuclear²

Los espectros de resonancia magnética nuclear fueron realizados en los siguientes equipos: Varian-UNITY-500, Varian-INOVA-400, Varian-MERCURY-400, Varian-INOVA-300 y Bruker-300. Los desplazamientos químicos se describen en partes por millón (δ) y las constantes de acoplamiento (J) se indican en hertzios (Hz). Los espectros de ¹H-RMN están referenciados respecto a la señal residual de protón del disolvente deuterado empleado en cada caso. La asignación de los distintos protones se hizo en base a experimentos bidimensionales tipo COSY, HSQC, HMBC y NOESY empleando la secuencia de pulsos estándar para cada uno de ellos. Cuando fue posible los protones diastereotópicos fueron designados con las letras α y β sin que deba considerarse como asignación estereoquímica de los mismos por analogía con la nomenclatura de esteroides. Los sistemas de spin complejos (2° orden; $\Delta\nu/J < 10$) fueron analizados como tales y las constantes de acoplamiento entre los distintos protones del sistema se calcularon cuando fue posible. Los espectros de ¹³C-RMN, desacoplados de protón en todos los casos, están referenciados respecto al desplazamiento químico de los correspondientes disolventes deuterados. La asignación de los distintos carbonos se hizo en algunos casos,

¹ W. C. Still; M. Khan; A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923-2925.

² T. D. W. Timothy en *High-resolution NMR techniques in organic chemistry*, Elsevier, **2009**.

basándose en experimentos bidimensionales tipo HSQC y HMBC. Si no se indica de otro modo, todos los espectros se registraron a temperatura ambiente.

Infrarrojo

Los espectros de infrarrojo (IR) se registraron en un espectrofotómetro modelo Perkin-Elmer-Spectrum One FT-IR. Las frecuencias del espectro se indican en cm^{-1} .

Espectros de masas

Los espectros de masa exacta de los compuestos fueron obtenidos con un espectrómetro de masas modelo Agilent 6520-Accurate-Mass LC/MS Q-TOF.

Puntos de fusión

Los puntos de fusión se midieron en una aparato de platina calentable tipo Kofler y están sin corregir.

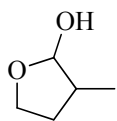
Rayos X

La difracción de rayos X se realizó en el Servicio Interdepartamental de Investigación (SIIdI) de la Universidad Autónoma de Madrid.

Microondas

Las reacciones llevadas a cabo en microondas se hicieron en un equipo CEM Discover equipado con agitación electromagnética y un sistema de control de la temperatura y la potencia.

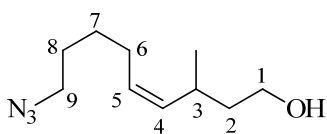
3.3.2.- Studies towards the total synthesis of lycopodine.



Synthesis of 3-methyltetrahydrofuran-2-ol (145): Diisobutylaluminium hydride (27.5 mL, 1.0 M solution in hexanes, 27.5 mmol) was added dropwise to a solution of 3-methyldihydrofuran-2(3*H*)-one (2.0 mL, 21.2 mmol) in CH_2Cl_2 (35 mL) at -78°C . The resulting solution was stirred at -78°C for one hour and then quenched with EtOAc. The reaction was warmed to room temperature and then poured into a solution of sat. aq. Na-K tartrate (100 mL). The resulting mixture was vigorously stirred until both the aqueous and the organic layers were clear (1 hour and 30 minutes). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 X 100 mL). The combined organic layers were dried over MgSO_4 , filtered and concentrated in vacuo. The crude lactol **145** (1.75 g, 81%) was used without further purification.

Wittig reaction. Synthesis of (Z)-9-azido-3-methylnon-4-en-1-ol (146).

Phosphonium salt **6** (6.7 mg, 14.7 mmol) was dissolved in dry CH_2Cl_2 (5 mL). THF (45 mL) was added and the solution was cooled to -78°C . Then KHMDS (29.4 mL, 14.7 mmol, 0.5 M solution in toluene) was added. After the reaction mixture was stirred for 30 minutes at -78°C , a solution of aldehyde **145** (1.0 g, 9.79 mmol) in dry THF (30 mL) was added dropwise over 25 minutes. After 1 hour, the reaction mixture was warmed to room temperature over 2 hours. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) yielded compound **146** as a colorless oil (1.2 mg, 61%).



$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 5.30 (m, 1H, H-5), 5.16 8(m, 1H, H-4), 3.59 (m, 2H, 2H-1), 3.25 (t, 2H, $J_{9,8} = 6.9$ Hz, 2H-9), 2.59 (m, 1H, H-3), 2.06 (m, 2H, 2H-6), 1.64-1.39 (m, 6H, 2H-2, 2H-7 and 2H-8), 0.95 (d, 3H, $J_{\text{CH}_3,3} = 6.7$ Hz, CH_3).

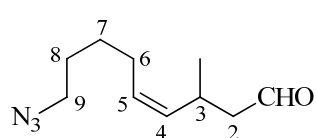
$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 136.3 (C-4), 128.3 (C-5), 61.4 (C-1), 51.4 (C-9), 40.2 (C-2), 28.7 (C-3), 28.5 (C-8), 26.9 (2C, C-6 and C-7), 21.5 (CH_3).

FTIR (neat) ν_{max} : 3351, 2930, 2870, 2097, 1456, 1247, 1052, 999, 851, 743 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{10}\text{H}_{20}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 198.1601, found: 198.1605

Oxidation of alcohol . Synthesis of (Z)-9-azido-3-methylnon-4-enal (147).

PCC (1.1 mg, 5.06 mmol) was added to a solution of **146** (500 mg, 2.53 mmol) in CH₂Cl₂ (20 mL) at room temperature. The mixture was stirred for 2 hours and then it was filtered through a plug of Celite. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) provided compound **147** as a colorless oil (395 mg, 80%).



¹H-NMR (300 MHz, CDCl₃): δ 9.68 (s, 1H, CHO), 5.26 (m, 2H, H-4 and H-5), 3.26 (t, 2H, *J*_{9,8} = 6.8 Hz, 2H-9), 3.02 (m, 1H, H-3), 2.35 (m, 2H, 2H-2), 2.08 (m, 2H, 2H-6), 1.65-1.36 (m, 4H, 2H-7 and 2H-8), 1.01 (d, 3H, *J*_{CH₃,3} = 6.7 Hz, CH₃).

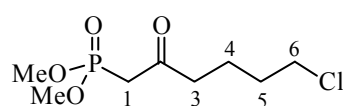
¹³C-NMR (75 MHz, CDCl₃): δ 201.9 (CHO), 134.5 (C-4), 129.0 (C-5), 51.5 (C-9), 51.0 (C-2), 28.6 (C-8), 27.1 (C-3), 26.9 2C, (C-7 and C-6), 21.3 (CH₃).

FTIR (neat) ν_{max}: 3003, 2933, 2872, 2825, 2721, 2097, 1725, 1457, 1374, 1351, 1248, 1125, 1078, 1007, 891, 746 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₀H₁₇N₃NaO [M+Na]⁺: 218.1264, found: 218.1266

Synthesis of dimethyl (6-chloro-2-oxohexyl)phosphonate (148).

A 1.6M solution of n-BuLi in hexanes (50 mL, 80 mmol) was added dropwise to a solution of dimethyl methylphosphonate (10 mL, 96 mmol) in THF (40 mL) at -78°C. After stirring for 30 minutes, methyl-5-chlorovalerate (6.0 g, 40 mmol) in THF (15 mL) was added over 20 minutes. The mixture was stirred for an additional 2 hours and then it was quenched with saturated solution of NH₄Cl. The solution was warmed to room temperature and extracted with EtOAc (3 X 50 mL). The organic layers were washed with brine, dried over MgSO₄ and concentrated in vacuo. The resulting oil was purified by column chromatography (silica gel, gradient from 1:1 hexanes/EtOAc to 95:5 EtOAc/MeOH) to obtain compound **148** as a colorless oil (8.73 g, 90%).



¹H-NMR (300 MHz, CDCl₃): δ 3.76 (d, 6H, *J*_{CH₃,P} = 11.2 Hz, CH₃O), 3.51 (t, 2H, *J*_{6,5} = 6.1 Hz, 2H-6), 3.07 (d, 2H, *J*_{1,P} = 22.8 Hz, 2H-1), 2.64 (t, 2H, *J*_{3,4} = 6.5 Hz, 2H-3), 1.74 (m, 4H, 2H-4 and 2H-5).

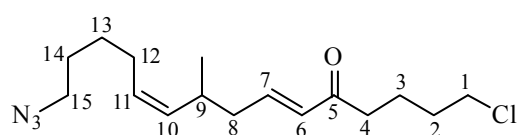
¹³C-NMR (75 MHz, CDCl₃): δ 201.3 (d, *J*_{C,P} = 6.4 Hz, C-2), 53.2 (d, 2C, *J*_{C,P} = 6.6 Hz, CH₃O), 44.7 (C-6), 43.1 (C-3), 41.5 (d, *J*_{C,P} = 128 Hz, C-1), 31.7 (C-5), 20.7 (C-4).

FTIR (neat) ν_{max}: 3469, 2958, 2854, 1716, 1449, 1405, 1375, 1259, 1185, 1031, 812 cm⁻¹.

HRMS-ESI (m/z): calcd for $C_8H_{17}ClO_4P$ $[M+H]^+$: 243.0547, found: 243.0539

Synthesis of (6*E*,10*Z*)-15-azido-1-chloro-9-methylpentadeca-6,10-dien-5-one (149).

A suspension of NaH (143 mg of 60% in mineral oil, 3.58 mmol) in dry THF (25 mL) was cooled to -78°C . Dimethyl (6-chloro-2-oxohexyl)phosphonate (compound **148**, 869 mg, 3.58 mmol) was added dropwise and the reaction mixture was stirred for 20 minutes at -78°C and 20 minutes at 0°C . Then a solution of **147** (350 mg, 1.79 mmol) in dry THF (10 mL) was added dropwise and the mixture was stirred for 30 minutes at 0°C . The reaction was warmed to room temperature and after 1 hour and 30 minutes it was quenched with water and extracted with Et_2O (3 X 30 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/ EtOAc) yielded compound **149** as a colorless oil (402 mg, 72%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 6.75 (dt, 1H, $J_{7,6} = 16.0$, $J_{7,8} = 7.4$ Hz, H-7), 6.07 (dt, 1H, $J_{6,7} = 16.0$, $J_{6,8} = 1.4$ Hz, H-6), 5.33 (m, 1H, H-11), 5.18 (m, 1H, H-10), 3.54 (t, 2H, $J_{1,2} = 6.2$ Hz, 2H-1), 3.26 (t, 2H, $J_{15,14} = 6.8$ Hz, 2H-15), 2.67-2.51 (m, 3H, H-9 and 2H-4), 2.17 (m, 2H, 2H-8), 2.04 (m, 2H, 2H-12), 1.77 (m, 4H, 2H-2 and 2H-3), 1.59 (m, 2H, 2H-14), 1.43 (m, 2H, 2H-13), 0.99 (d, 3H, $J_{\text{CH}_3,9} = 6.6$ Hz, CH_3).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 199.8 (C-5), 145.8 (C-7), 135.2 (C-10), 131.4 (C-6), 128.8 (C-11), 51.5 (C-15), 44.8 (C-1), 40.4 (C-8), 39.2 (C-4), 32.1 (C-2), 31.6 (C-9), 28.6 (C-14), 27.1 (C-12), 26.9 (C-13), 21.6 (C-3), 21.2 (CH_3).

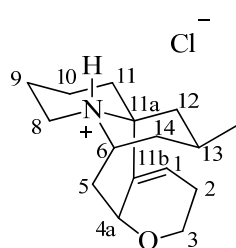
FTIR (neat) ν_{max} : 3369, 2956, 2930, 2870, 2097, 1698, 1673, 1630, 1456, 1373, 1276, 1060, 981 cm^{-1} .

HRMS-ESI (m/z): calcd for $C_{16}H_{27}ClN_3O$ $[M+H]^+$: 318.1237, found: 318.1247

Synthesis of *rac*-(6*R*,7*S*,11*aS*,13*S*)-13-methyl-1,2,3,5,6,7,8,9,10,11-decahydro-6,11a-propanopyrano[3,2-*a*]quinolizin-7-ium chloride (154).

A solution of compound **149** (70 mg, 0.22 mmol) and KI (65 mg, 0.40 mmol) in DMF/ EtOH (10 mL, 4:1) was heated in a microwave reactor at 140°C for 3 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, gradient from CH_2Cl_2 to 97:3

CH₂Cl₂/MeOH) to yield compound **153** as a yellow solid (31 mg, 57%). The relative stereochemistry of **153** was confirmed by X-ray crystallographic.³



¹H-NMR (500 MHz, CDCl₃): δ 4.16 (dtd, 1H, $J = 10.7$, $J = 3.8$, $J = 1.2$ Hz, H-3 α), 3.84 (m, 1H, H-3 β), 3.53 (dddd, 1H, $J = 13.6$, $J = 7.1$, $J = 3.7$, $J = 1.7$ Hz, H-6), 3.11 (m, 2H, 2H-8), 2.60 (dd, 1H, $J_{5\alpha,5\beta} = 17.9$, $J_{5\alpha,6} = 8.1$ Hz, H-5 α), 2.53-2.37 (m, 2H, H-9 α and H-14 α), 2.11-1.92 (m, 4H, H-1 α , H-2 α , H-5 β and H-11 α), 1.91-1.81 (m, 4H, H-1 β , H-2 β , H-12 α and H-13), 1.79-1.69 (m, 3H, H-9 β , H-10 α and H-11 β), 1.68-1.59 (m, 2H, H-12 β and H-14 β), 1.38 (m, 1H, H-10 β), 0.97 (d, 3H, $J_{CH_3,13} = 6.0$ Hz, CH₃).

¹³C-NMR (125 MHz, CDCl₃): δ 146.8 (C-4a), 100.8 (C-11b), 65.7 (C-3), 62.2 (C-11a), 55.2 (C-6), 48.7 (C-8), 41.9 (C-12), 38.5 (C-14), 31.9 (C-1), 28.3 (C-5), 22.6 (3C, C-2, C-9 and C-13), 20.3 (CH₃), 19.4 (C-11), 19.2 (C-10).

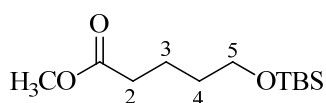
FTIR (KBr) ν_{\max} : 3400, 2931, 2871, 2586, 1683, 1441, 1387, 1248, 1192, 1103, 1048, 986, 951, 925, 729 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₆H₂₆NO [M+H]⁺: 248.2009, found: 248.2016

Mp: 180-182°C

Synthesis of methyl 5-[(*tert*-butyldimethylsilyl)oxy]pentanoate (**155**).

To a solution of δ -valerolactone (5 g, 50 mmol) in MeOH (50 mL) was added concentrated H₂SO₄ (5 drops). The reaction was heated at reflux for 5 hours. Then it was cooled in an ice-salt bath and NaHCO₃ (600 mg) was added. The mixture was allowed to stir for 10 minutes and for 2 hours in the freeze. The cold mixture was filtered and the solvent was removed in vacuo. The residue was dissolved in CH₂Cl₂ (50 mL), cooled to 0°C, and TBDMSCl (8.8 g, 58.5 mmol) and imidazole (8.9 g, 130 mmol) were added. The reaction mixture was allowed to stir while warming to room temperature overnight. The mixture was diluted with H₂O and the layers were separated. The organic layer was washed with water, twice with saturated aqueous CuSO₄, brine, dried over MgSO₄ and concentrated. The residue was purified by flash column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) to obtain compound **155** (9.86 g, 80%, 2 steps) as a colorless oil.



¹H-NMR (300 MHz, CDCl₃): δ 3.63 (s, 3H, CH₃O), 3.61 (t, 2H, $J_{5,4} = 6.2$ Hz, 2H-5), 2.32 (t, 2H, $J_{2,3} = 7.4$ Hz, 2H-2), 1.67 (m, 2H,

³ Los datos de difracción de rayos X del compuesto **153** se encuentran en el anexo II.

2H-3), 1.54 (m, 2H, 2H-4), 0.88 (s, 9H, OSi(CH₃)₂C(CH₃)₃), 0.03 (6H, OSi(CH₃)₂C(CH₃)₃).

¹³C-NMR (75 MHz, CDCl₃): δ 174.2 (C=O), 62.8 (C-5), 51.6 (OCH₃), 34.0 (C-4), 32.3 (C-2), 26.2 (3C, OSi(CH₃)₂C(CH₃)₃), 21.6 (C-3), 18.5 (OSi(CH₃)₂C(CH₃)₃), -5.2 (2C, OSi(CH₃)₂C(CH₃)₃).

FTIR (neat) v_{max}: 2953, 2930, 2858, 1743, 1472, 1463, 1436, 1388, 1361, 1254, 1167, 1098, 1006, 837, 776 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₂H₂₇O₃Si [M+H]⁺: 247.1724, found: 247.1716

Synthesis of dimethyl {6-[(*tert*-butyldimethylsilyl)oxy]-2-oxohexyl}phosphonate (**156**).

A 1.6M solution of n-BuLi in hexanes (20.2 mL, 32.4 mmol) was added dropwise to a solution of dimethyl methylphosphonate (4.1 mL, 38.9 mmol) in THF (40 mL) at -78°C. After stirring for 30 minutes, **155** (4.0 g, 16.2 mmol) in THF (15 mL) was added over 20 minutes. The mixture was stirred for an additional 2 hours and then it was quenched with saturated solution of NH₄Cl. The solution was warmed to room temperature and extracted with EtOAc (3 X 40 mL). The organic layers were washed with brine, dried over MgSO₄ and concentrated in vacuo. The resulting oil was purified by column chromatography (silica gel, gradient from 1:1 hexanes/EtOAc to 95:5 EtOAc/MeOH) to obtain compound **156** as a colorless oil (4.6 g, 85%).

¹H-NMR (300 MHz, CDCl₃): δ 3.77 (d, 6H, *J*_{CH₃,P} = 11.2 Hz, CH₃O), 3.58 (t, 2H, *J*_{6,5} = 6.2 Hz, 2H-6), 3.06 (d, 2H, *J*_{1,P} = 22.7 Hz, 2H-1), 2.62 (m, 2H, 2H-3), 1.62 (m, 2H, 2H-4), 1.49 (m, 2H, 2H-5), 0.86 (s, 9H, OSi(CH₃)₂C(CH₃)₃), 0.02 (6H, OSi(CH₃)₂C(CH₃)₃).

¹³C-NMR (75 MHz, CDCl₃): δ 202.1 (C-2), 61.2 (C-6), 53.4 (d, 2C, *J*_{C,P} = 6.0 Hz, CH₃O), 43.9 (C-3), 41.3 (d, *J*_{C,P} = 129 Hz, C-1), 25.7 (3C, OSi(CH₃)₂C(CH₃)₃), 24.9 (C-5), 19.7 (C-4), 18.8 (OSi(CH₃)₂C(CH₃)₃), -3.6 (2C, OSi(CH₃)₂C(CH₃)₃).

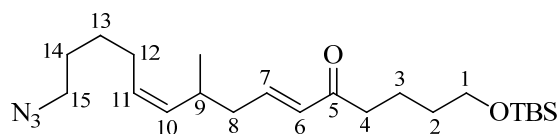
FTIR (neat) v_{max}: 3410, 2955, 2872, 1714, 1458, 1403, 1373, 1247, 1185, 1027, 816 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₄H₃₂O₅PSi [M+H]⁺: 339.1751, found: 339.1742

Synthesis of (6*E*,10*Z*)-15-azido-1-((*tert*-butyldimethylsilyl)oxy)-9-methylpentadeca-6,10-dien-5-one (**157**).

A suspension of NaH (164 mg of 60% in mineral oil, 4.1 mmol) in dry THF (25 mL) was cooled to -78°C. Dimethyl {6-[(*tert*-butyldimethylsilyl)oxy]-2-oxohexyl}phosphonate

(compound **156**, 1387 mg, 4.1 mmol) was added dropwise and the reaction mixture was stirred for 20 minutes at -78°C and 20 minutes at 0°C . Then a solution of **147** (400 mg, 2.05 mmol) in dry THF (10 mL) was added dropwise and the mixture was stirred for 30 minutes at 0°C . The reaction was warmed to room temperature and after 1 hour and 30 minutes it was quenched with water and extracted with Et_2O (3 X 30 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/ EtOAc) yielded compound **157** as a colorless oil (618 mg, 74%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 6.74 (dt, 1H, $J_{7,6} = 15.8$, $J_{7,8} = 7.4$ Hz, H-7), 6.07 (dt, 1H, $J_{6,7} = 15.8$, $J_{6,8} = 1.4$ Hz, H-6), 5.34 (m, 1H, H-11), 5.18 (m, 1H, H-10), 3.61 (t, 2H, $J_{1,2} = 6.2$

Hz, 2H-1), 3.27 (t, 2H, $J_{15,14} = 6.7$ Hz, 2H-15), 2.59 (m, 1H, H-9), 2.54 (t, 2H, $J_{4,3} = 7.3$ Hz, 2H-4), 2.16 (m, 2H, 2H-8), 2.05 (m, 2H, 2H-12), 1.72-1.37 (m, 8H, 2H-2, 2H-3, 2H-13 and 2H-14), 0.99 (d, 3H, $J_{\text{CH}_3,9} = 6.7$ Hz, CH_3), 0.89 (s, 9H, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 0.04 (s, 6H, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$).

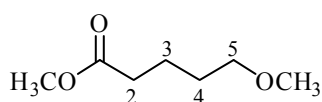
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 200.6 (C-5), 145.5 (C-7), 135.3 (C-10), 131.5 (C-6), 128.7 (C-11), 63.0 (C-1), 51.5 (C-15), 40.4 (C-8), 40.0 (C-4), 32.5 (C-9), 31.6 (C-2), 28.6 (C-14), 27.1 (C-12), 27.0 (C-13), 26.1 (3C, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 21.2 (CHCH_3), 20.9 (C-3), 18.5 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), -5.2 (2C, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$).

FTIR (neat) ν_{max} : 2954, 2930, 2858, 2096, 1698, 1675, 1631, 1471, 1461, 1360, 1255, 1102, 1006, 979, 836, 776 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{22}\text{H}_{42}\text{N}_3\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$: 408.3041, found: 408.3042

Synthesis of methyl 5-methoxypentanoate (**159**).

Sulfuric acid (0.1 mL, 1.5 mmol) was added to a stirred solution of δ -valerolactone (3.0 g, 30 mmol), trimethyl orthoformate (4.9 mL, 45 mmol), and methanol (30 mL). The mixture was heated at 50°C for 12 hours. At this time the solvent was removed and then saturated solution of NaHCO_3 was added. The mixture was extracted with AcOEt (3 X 40 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo to obtain compound **159** as a colorless oil (3.9 g, 90%).



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 3.66 (s, 3H, CH_3OCO), 3.37 (t, 2H, $J_{5,4} = 6.2$ Hz, 2H-5), 3.35 (s, 3H, CH_3O), 2.33 (t, 2H, $J_{2,3} = 7.3$

Hz, 2H-2), 1.75-1.52 (m, 4H, 2H-3 and 2H-4).

^{13}C -NMR (75 MHz, CDCl_3): δ 173.4 (C-1), 72.0 (C-5), 58.1 (CH_3O), 51.0 (CH_3OCO), 33.5 (C-2), 28.8 (C-4), 21.5 (C-3).

FTIR (neat) ν_{max} : 2035, 1732, 1439, 1158, 1103, 1066 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_7\text{H}_{15}\text{O}_3$ $[\text{M}+\text{H}]^+$: 147.1016, found: 147.1015

Synthesis of dimethyl (6-methoxy-2-oxohexyl)phosphonate (**160**).

A 1.6M solution of n-BuLi in hexanes (42.7 mL, 68.4 mmol) was added dropwise to a solution of dimethyl methylphosphonate (7.7 mL, 71.8 mmol) in THF (40 mL) at -78°C . After stirring for 30 minutes, **159** (5 g, 34.2 mmol) in THF (15 mL) was added over 20 minutes. The mixture was stirred for an additional 2 hours and then it was quenched with saturated solution of NH_4Cl . The solution was warmed to room temperature and extracted with EtOAc (3 X 40 mL). The organic layers were washed with brine, dried over MgSO_4 and concentrated in vacuo. The resulting oil was purified by column chromatography (silica gel, gradient from 1:1 hexanes/EtOAc to 95:5 EtOAc/MeOH) to obtain compound **160** as a colorless oil (6.7 g, 83%).

^1H -NMR (300 MHz, CDCl_3): δ 3.76 (d, 6H, $J_{\text{CH}_3,\text{P}} = 11.2$ Hz, $(\text{CH}_3\text{O})_2\text{PO}$), 3.34 (t, 2H, $J_{6,5} = 6.1$ Hz, 2H-6), 3.29 (s, 3H, CH_3O), 3.06 (d, 2H, $J_{1,\text{P}} = 22.7$ Hz, 2H-1), 2.63 (t, 2H, $J_{3,4} = 7.0$ Hz, 2H-3), 1.70-1.50 (m, 4H, 2H-4 and 2H-5).

^{13}C -NMR (75 MHz, CDCl_3): δ 201.8 (d, $J_{\text{C},\text{P}} = 6$ Hz, $\text{C}=\text{O}$), 72.4 (C-6), 58.6 (CH_2OCH_3), 53.1 (d, 2C, $J_{\text{C},\text{P}} = 6$ Hz, $(\text{CH}_3\text{O})_2\text{PO}$), 43.9 (C-3), 41.4 (d, $J_{\text{C},\text{P}} = 128$ Hz, C-1), 28.9 (C-5), 20.3 (C-4).

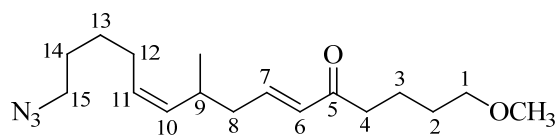
FTIR (neat) ν_{max} : 3483, 2956, 2857, 1715, 1459, 1401, 1255, 1185, 1118, 1031, 820 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_9\text{H}_{20}\text{O}_5\text{P}$ $[\text{M}+\text{H}]^+$: 239.1043, found: 239.1048

Synthesis of (6E,10Z)-15-azido-1-methoxy-9-methylpentadeca-6,10-dien-5-one (**161**).

A suspension of NaH (164 mg of 60% in mineral oil, 4.1 mmol) in dry THF (25 mL) was cooled to -78°C . Dimethyl (6-methoxy-2-oxohexyl)phosphonate (compound **160**, 976 mg, 4.1 mmol) was added dropwise and the reaction mixture was stirred for 20 minutes at -78°C and 20 minutes at 0°C . Then a solution of **147** (400 mg, 2.05 mmol) in dry THF (10 mL) was added dropwise and the mixture was stirred for 30 minutes at 0°C . The reaction was warmed to room temperature and after 1 hour and 30 minutes it was quenched with water and extracted with

Et₂O (3 X 30 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) yielded compound **161** as a colorless oil (517 mg, 82%).



¹H-NMR (300 MHz, CDCl₃): δ 6.74 (dt, 1H, $J_{7,6} = 15.8, J_{7,8} = 7.4$ Hz, H-7), 6.07 (dt, 1H, $J_{6,7} = 15.8, J_{6,8} = 1.4$ Hz, H-6), 5.32 (m, 1H, H-11), 5.17 (m, 1H, H-10), 3.37 (t, 2H, $J_{1,2} = 6.1$ Hz,

2H-1), 3.31 (s, 3H, OCH₃), 3.26 (t, 2H, $J_{15,14} = 6.8$ Hz, 2H-15), 2.66-2.50 (m, 3H, 2H-4 and H-9), 2.16 (m, 2H, 2H-8), 2.04 (m, 2H, 2H-12), 1.74-1.52 (m, 6H, 2H-2, 2H-3 and 2H-14), 1.43 (m, 2H, 2H-13), 0.98 (d, 3H, $J_{CH_3,9} = 6.6$ Hz, CHCH₃).

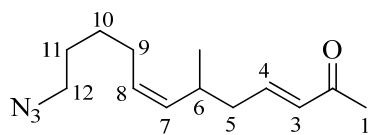
¹³C-NMR (75 MHz, CDCl₃): δ 200.4 (C=O), 145.5 (C-7), 135.5 (C-10), 131.5 (C-6), 128.7 (C-11), 72.6 (C-1), 58.7 (OCH₃), 51.5 (C-15), 40.3 (C-8), 39.9 (C-4), 31.6 (C-9), 29.3 (C-2), 28.6 (C-14), 27.1 (C-12), 26.9 (C-13), 21.2 (CHCH₃), 21.1 (C-3).

FTIR (neat) ν_{max} : 2930, 2868, 2096, 1697, 1673, 1630, 1457, 1248, 1120, 981 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₇H₃₀N₃O₂ [M+H]⁺: 308.2333, found: 308.2322

Synthesis of (3E,7Z)-12-azido-6-methyldodeca-3,7-dien-2-one (**163**).

To a solution of **147** (180 mg, 0.92 mmol) in CH₂Cl₂ (20 mL) was added 1-(triphenylphosphoranylidene)-2-propanone (879 mg, 2.76 mmol) at room temperature and the mixture was stirred for 3 days. The solvent was removed and the crude product was purified by column chromatography (silica gel, gradient from hexanes to 90:10 hexanes/EtOAc) to provide compound **163** as a colorless oil (176 mg, 82%).



¹H-NMR (300 MHz, CDCl₃): δ 6.72 (dt, 1H, $J_{4,3} = 15.8, J_{4,5} = 7.3$ Hz, H-4), 6.05 (dt, 1H, $J_{3,4} = 15.8, J_{3,5} = 1.4$ Hz, H-3), 5.33 (m, 1H, H-8), 5.18 (m, 1H, H-7), 3.26 (t, 2H, $J_{12,11} = 6.8$ Hz, 2H-12), 2.61 (m, 1H, H-6), 2.22 (s, 3H, 3H-1), 1.59-1.97 (m, 4H, 2H-5 and 2H-9), 1.59 (m, 2H, 2H-11), 1.42 (m, 2H, 2H-10), 0.99 (d, 3H, $J_{CH_3,6} = 6.7$ Hz, CHCH₃).

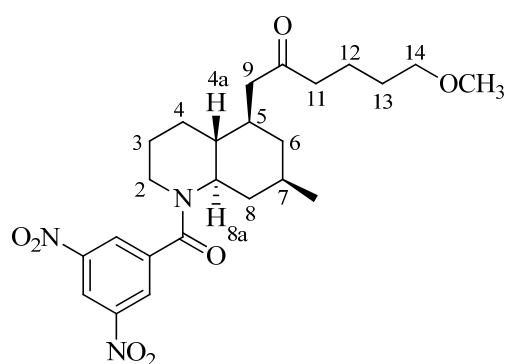
¹³C-NMR (75 MHz, CDCl₃): δ 198.7 (C-2), 146.7 (C-4), 135.2 (C-7), 132.5 (C-3), 128.8 (C-8), 51.5 (C-12), 40.3 (C-9), 31.6 (C-6), 28.6 (C-11), 27.1 (C-9), 27.0 (C-1), 26.9 (C-10), 21.2 (CHCH₃).

FTIR (neat) ν_{max} : 3009, 2932, 2860, 2097, 1698, 1674, 1628, 1454, 1362, 1249, 723 cm⁻¹.

HRMS-ESI (m/z): calcd for C₁₃H₂₂N₃O [M+H]⁺: 236.1757, found: 236.1755

Synthesis of *rac*- 1-[(4a*R*,5*R*,7*R*,8a*R*)-1-(3,5-dinitrobenzoyl)-7-methyldecahydroquinolin-5-yl]-6-methoxyhexan-2-one (167).

A solution of compound **160** (70 mg, 0.23 mmol) in dry MeOH (10 mL) was heated in a microwave reactor at 140°C for 3 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude material was dissolved in absolute ethanol (8 mL), cooled to 0°C and sodium borohydride (13 mg, 0.35 mmol) was added. After 1 hour the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 X 30 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated in vacuo. The crude oil was dissolved in CH₂Cl₂ (8 mL), cooled to 0°C and Et₃N (0.06 mL, 0.46 mmol) and 3,5-dinitrobenzoyl chloride (80 mg, 0.35 mmol) were added sequentially. After stirring at room temperature for 10 hours the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 X 15 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) to afford compound **163** (22 mg, 20%, 3 steps) as a yellow solid.



¹H-NMR (500 MHz, CDCl₃): δ 9.07 (m, 1H, Ar-H), 8.57 (dd, 2H, $J = 2.1$, $J = 0.5$ Hz, Ar-H), 3.62 (td, 1H, $J = 11.3$, $J = 3.3$ Hz, H-8a), 3.43-3.24 (m, 4H, 2H-2 and 2H-14), 3.32 (s, 3H, OCH₃), 2.58 (dd, 1H, $J_{9\alpha,9\beta} = 16.5$, $J_{9\alpha,5} = 4.3$ Hz, H-9 α), 2.44 (m, 2H, 2H-11), 2.22 (m, 2H, H-9 β and H-8 α), 1.84 (m, 2H, H-4 α and H-5), 1.78-1.52 (m, 8H, 2H-3, H-6 α , H-7, 2H-12 and 2H-13), 1.47 (m, 1H, H-

4a), 1.30 (m, 1H, H-8 β), 1.15 (m, 1H, H-4 β), 0.94 (d, 3H, $J_{\text{CH}_3,7} = 6.3$ Hz, CHCH₃), 0.79 (m, 1H, H-6 β).

¹³C-NMR (125 MHz, CDCl₃): δ 210.2 (C=O, ketone), 166.4 (C=O amide), 148.6 (2C, Ar-C), 140.8 (Ar-C), 127.4 (2C, Ar-C), 119.4 (Ar-C), 72.6 (C-14), 61.3 (C-8a), 58.7 (OCH₃), 46.7 (C-9), 43.5 (2C, C-2 and C-11), 41.8 (C-4a), 41.6 (C-6), 38.2 (C-8), 37.7 (C-5), 31.2 (C-7), 29.3 (C-13), 24.0 (C-3), 23.7 (C-4), 22.1 (CHCH₃), 20.7 (C-12).

FTIR (KBr) ν_{max} : 3103, 2927, 1869, 1713, 1634, 1543, 1461, 1432, 1344, 1275, 1117, 1080, 919, 730 cm⁻¹.

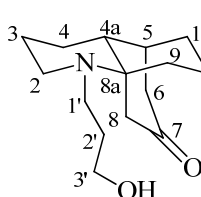
HRMS-ESI (m/z): calcd for C₂₄H₃₄N₃O₇ [M+H]⁺: 476.2391, found: 476.2401

Mp: 53-55°C

3.3.3.- Synthesis of 15-desmethyl lycopodine.

Synthesis of *rac*-(4a*R*,5*S*,8a*S*)-1-(3-hydroxypropyl)hexahydro-1*H*-5,8a-propanoquinolin-7(8*H*)-one (**168**).

K₂CO₃ (118 mg, 0.86 mmol), NaHCO₃ (115 mg, 1.36 mmol) and, 3-iodo-1-propanol (0.06 mL, 0.59 mmol) were added to a solution of amine **143** (75 mg, 0.39 mmol) in acetone (4 mL). The reaction mixture was heated to reflux. After 6 hours, the reaction was cooled to room temperature and the solvent was removed in vacuo. The reaction mixture was purified by chromatography (silica gel, gradient from CH₂Cl₂ to 95:5 CH₂Cl₂/MeOH) to afford compound **168** (66 mg, 67%) as a brown solid.



¹H-NMR (MHz, CDCl₃): δ 3.77 (m, 2H, 2H-3'), 3.13-3.00 (m, 2H, H-2α and H-1'α), 2.66 (d, 1H, *J*_{8α,8β} = 16.5 Hz, H-8α), 2.49 (dd, 1H, *J*_{6α,6β} = 17.1, *J*_{6α,5} = 6.6 Hz, H-6α), 2.30-2.07 (m, 6H, H-1'β, H-2β, H-6β, H-8β, H-9α and H-4a), 1.92 (m, 1H, H-2'α), 1.79 (m, 1H, H-3α), 1.73-1.58 (m, 5H, H-5, 2H-11, H-3β and H-10α), 1.57-1.47 (m, 3H, 2H-4 and H-9β), 1.47-1.29 (m, 2H, H-2'β and H-10β).

¹³C-NMR (MHz, CDCl₃): δ 212.6 (C=O), 64.5 (C-3'), 59.5 (C-8a), 48.5 (C-1'), 46.9 (C-2), 44.3 (C-5), 42.2 (C-6), 39.0 (C-8), 38.1 (C-9), 35.8 (C-4a), 32.9 (C-11), 27.8 (C-2'), 26.1 (C-4), 25.6 (C-3), 19.6 (C-10).

FTIR (KBr) ν_{max}: 3384, 2931, 2874, 1703, 1468, 1443, 1416, 1336, 1253, 1231, 1172, 1125, 1111, 1067, 733 cm⁻¹.

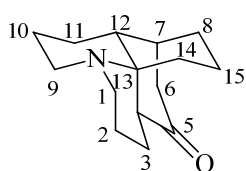
HRMS-ESI (m/z): calcd for C₁₅H₂₆NO₂ [M+H]⁺: 252.1958, found: 252.1962

Mp: 85-87°C

Synthesis of *rac*-(1*S*,8a*R*,9*S*,12a*R*)-dodecahydro-1,9-ethanopyrido[2,1-*j*]quinolin-14-one (15-desmethyl lycopodine) (**170**).

To a Schlenk tube was added compound **168** (35 mg, 0.14 mmol), tBuOK (94 mg, 0.84 mmol), benzophenone (457 mg, 2.52 mmol) and 3 mL of dry toluene. The mixture was subjected to three cycles of freeze-pump-thaw degas protocol and was sealed and heated at 110°C for 1 hour. After cooling to room temperature, the reaction was quenched by addition of 5 mL of 5% HCl solution and the mixture was extracted with ether (2 X 10 mL). The aqueous layer was neutralized with Na₂CO₃ powder until pH 11 was reached and the solution was extracted with CH₂Cl₂ (5 X 15 mL). The combined

organic layers were dried over MgSO_4 , filtered and concentrated. The crude enone was then dissolved in 3 mL of MeOH. Pt_2O (6 mg) was added and the mixture was stirred under 1 atm of H_2 at room temperature for 12 hours. The resulting reaction crude was filtered through a pad of Celite and the filtrate was concentrated. Flash chromatography of the residue (silica gel, gradient from CH_2Cl_2 to 92:8 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) yielded compound **170** as a white solid (20 mg, 62%).



$^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 3.46 (td, 1H, $J = 14.1$, $J = 3.6$ Hz, H-1 α), 3.26 (td, 1H, $J = 12.7$, $J = 3.2$ Hz, H-9 α), 2.87 (m, 2H, H-4 and H-9 β), 2.67-2.54 (m, 2H, H-1 β and H-8 α), 2.57 (dd, 1H, $J_{6\alpha,6\beta} = 16.2$, $J_{6\alpha,7} = 6.3$ Hz, H-6 α), 2.25 (dd, 1H, $J_{6\beta,6\alpha} = 16.2$, $J_{6\beta,7} = 1.5$ Hz, H-6 β), 2.18-2.10 (m, 2H, H-3 α and H-12), 2.02 (m, 1H, H-7), 1.93-1.57 (m, 11H, 2H-2, H-3 β , H-8 β , 2H-10, 2H-11, 2H-14 and H-15 α), 1.28 (m, 1H, H-15 β).

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3): δ 213.2 (C=O), 59.9 (C-13), 47.5 (C-9), 46.7 (C-1), 44.1 (C-7), 43.3 (C-4), 42.5 (C-6), 36.5 (C-12), 33.1 (2C, C-8 and C-14), 24.6 (2C, C-10 and C-11), 19.3 (C-15), 18.8 (C-3), 18.6 (C-2).

FTIR (KBr) ν_{max} : 2931, 2877, 2529, 1702, 1469, 1450, 1417, 1315, 1167, 1115, 1105, 978, 803, 735 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{15}\text{H}_{24}\text{NO}$ $[\text{M}+\text{H}]^+$: 234.1852, found: 234.1851

Mp: 68-70°C

Capítulo 4

SÍNTESIS TOTAL DE LA AMFOROGININA C

4.1.- INTRODUCCIÓN.

La síntesis total de productos naturales es un área central dentro de la química orgánica.¹ Las interesantes propiedades biológicas de los compuestos encontrados en la naturaleza junto a la dificultad para obtener cantidades suficientes de los mismos de sus fuentes naturales que permitan su más amplio estudio y aplicación, ha hecho necesario desarrollar rutas de síntesis a partir de moléculas más sencillas y accesibles. Nuestro grupo de investigación ha trabajado también en este campo² y a continuación se presenta la primera síntesis total de la amforoginina C (Figura 4.1).

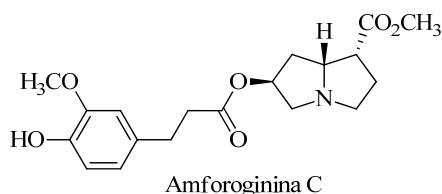


Figura 4.1. Estructura de la amforoginina C.

La amforoginina C pertenece a la gran familia de los alcaloides pirrolizidínicos, compuestos caracterizados por contener en su estructura un anillo de pirrolizidina. Estos productos se encuentran en la naturaleza en más de 6000 plantas de diferentes familias que los sintetizan para su defensa frente a herbívoros.³ Desde hace años son conocidas numerosas actividades biológicas de los alcaloides de pirrolizidina destacando especialmente la hepatotoxicidad,⁴ ya que de los más de 660 compuestos de esta familia identificados hasta la fecha, más de la mitad son tóxicos para el hígado.⁵ De hecho los alcaloides pirrolizidínicos son unos de los compuestos tóxicos más comunes producidos por las plantas y han sido responsables de numerosas intoxicaciones de ganado⁶ e incluso de humanos al consumir éstos plantas medicinales o alimentos contaminados tales como miel o leche.⁷

¹ a) K. C. Nicolau, D. Vourloumis, N. Winssinger and P. S. Baran, *Angew. Chem. Int. Ed.* **2000**, 39, 44-122; b) K. C. Nicolau, E. J. Sorensen, en *Classics in Total Synthesis*, Wiley, **1996**; c) K. C. Nicolau, S. A. Snyder en *Classics in Total Synthesis II*, Wiley, **2003**; d) K. C. Nicolau, J. S. Chen en *Classics in Total Synthesis III*, Wiley, **2011**.

² F. Sánchez-Sancho, B. Herradón, *Tetrahedron Asymmetry* **1998**, 9, 1951-1965.

³ T. Hartmann, D. Ober, *Topics Curr. Chem.* **2002**, 209, 207-243.

⁴ M. Dreger, M. Stanislawski, A. Krajewska-Patan, S. Mielcarek, P. L. Mikolajczak, W. Buchwald, *Herba Pol.* **2009**, 55, 27-146.

⁵ La hepatotoxicidad está por lo general asociada a una insaturación entre los carbonos C1 y C2 del anillo de pirrolizidina.

⁶ a) V. M. T. Nobre, A. F. M. Dantas, F. Riet-Correa, J. M. Barbosa Filho, I. M. Tabosa, J. S. Vasconcelos, *Toxicon*, **2005**, 45, 347-352; b) M. T. Fletcher, R. A. McKenzie, B. J. Blaney, K.G. Reichmann, *J. Agric. Food Chem.* **2009**, 57, 311-319.

⁷ a) N. Bach, S. N. Thung, F. Schaffner, *Am. J. Med.* **1989**, 87, 97-99; b) W. Sperl, H. Stuppner, J. Gassner, W. Judmaier, O. Dietze, W. Vogel, *Eur. J. Pediatr.* **1995**, 154, 112-116; c) R. A. Coulombe, *Adv. Food. Nutr. Res.* **2003**, 45, 61-99.

Además han sido descritas también otras actividades biológicas de estos alcaloides. Por ejemplo, se ha visto que la cremastrina, aislada en 1995 de un tubérculo japonés empleado en medicina tradicional,⁸ actúa como antagonista de un receptor muscarínico de la acetilcolina⁹ (Figura 4.2). Así mismo es conocido que la alexina, aislada de *Alexa canaracunensis*¹⁰ y la casuarina, aislada por primera vez de *Casuarina equisetifolia*,¹¹ son inhibidores de glicosidasas y poseen actividad antiviral y antibacteriana.¹²

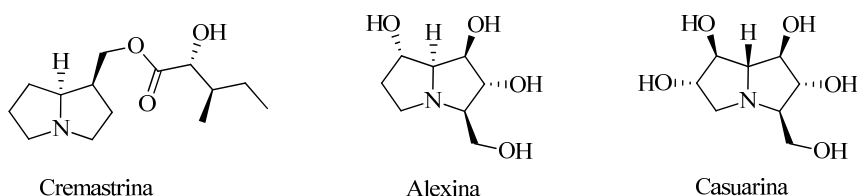


Figura 4.2. Algunos alcaloides de pirrolizidina con actividad biológica.

En cuanto a la amforoginina C, ésta pertenece a la familia de las amforogininas descubiertas en 1998 por el grupo de País¹³ del *Institut de Chimie des Substances Naturelles* en Francia (Figura 4.3). Estos compuestos fueron aislados de las hojas de la planta *Amphorogyne spicata* (Santalaceae) de Nueva Caledonia y se caracterizan por estar sustituidos únicamente en las posiciones C-1 y C-6 del anillo de pirrolizidina, lo cual no había sido identificado anteriormente en los alcaloides de pirrolizidina.

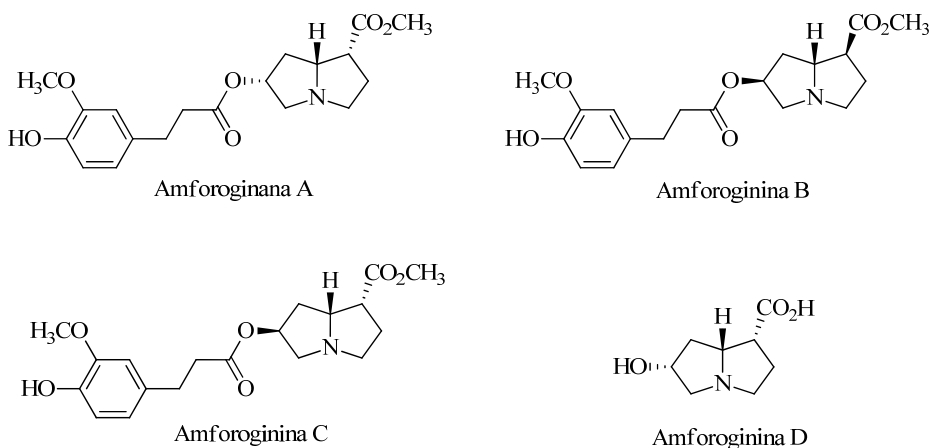


Figura 4.3 Amforogininas A-D.

⁸ Y. Ikeda, H. Nonaka, T. Furumai, I. J. Igarashi, *J. Nat. Prod.* **2005**, 68, 572-573.

⁹ K. N. Hahn, O. O. Fadeyi, H. P. Cho, C. W. Lindsley, *Tetrahedron Lett.* **2012**, 53, 3577-3580.

¹⁰ R. J. Nash, L. E. Fellows, J. V. Dring, G. W. J. Fleet, A. E. Derome, T. A. Hamor, A. M. Scofield, D. J. Watkin, *Tetrahedron Lett.* **1988**, 29, 2487-2490.

¹¹ R. J. Nash, P. I. Thomas, R. D. Waigh, G. W. J. Fleet, M. R. Wormald, P. M. de Q. Lilley, D. J. Watkin, *Tetrahedron Lett.* **1994**, 35, 7849-7852.

¹² N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron Asymmetry*, **2000**, 11, 1645-1680.

¹³ D. T. T. Huong, M.-T. Martin, M. Litaudon, T. Sévenet, M. País, *J. Nat. Prod.* **1998**, 61, 1444-1446.

4.2.- ANTECEDENTES.

4.2.1.- Antecedentes en la síntesis de amforogininas.

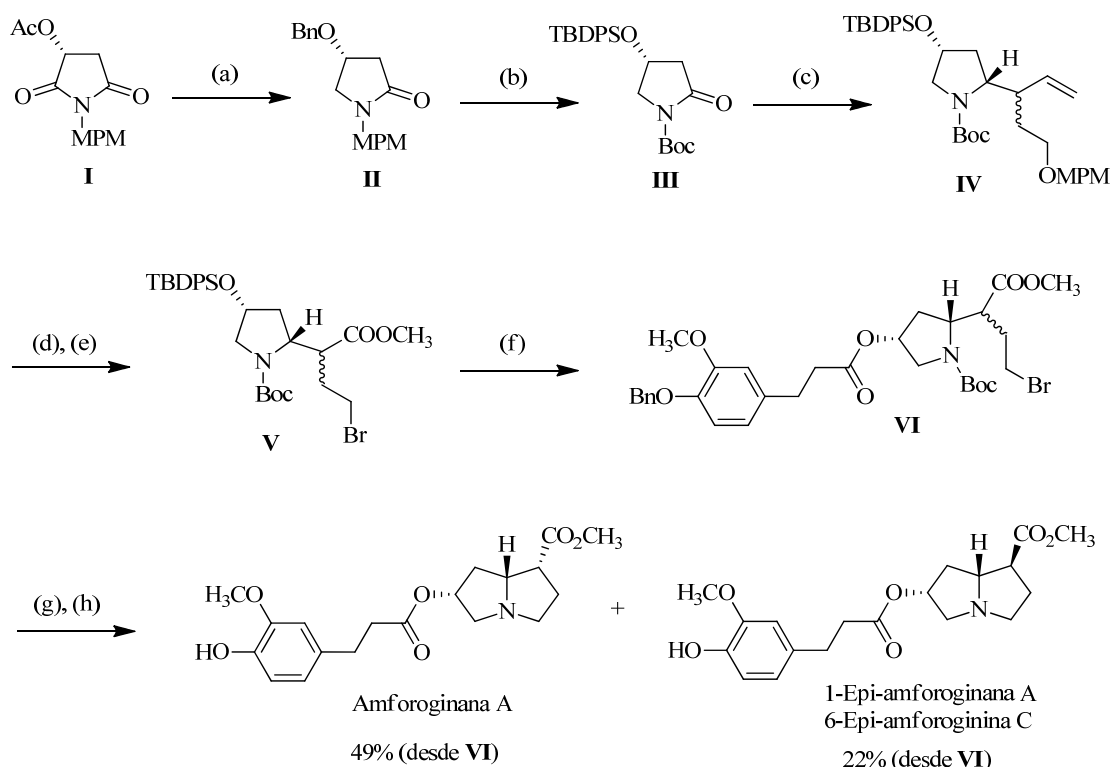
La síntesis de la amforoginina C descrita en esta tesis es la primera para este producto natural, si bien anteriormente se han publicado dos síntesis de la amforoginina A y una de la amforoginina D.

Primeramente el grupo de Yoda en Japón publicó la preparación de la amforoginina A en 2003.¹⁴ Para ello parte como punto de partida del compuesto **I** (Esquema 4.1), previamente descrito en la literatura y que puede ser preparado desde el ácido D-málico. Una reducción estereoselectiva, desoxigenación y posterior intercambio del grupo acetoxi por benciloxi conduce al compuesto **II**. A continuación se sintetiza el intermedio **III** mediante un cambio de grupos protectores. El siguiente paso es un acoplamiento entre el ion iminio derivado de la correspondiente α -hidroxipirrolidina y el aliltrimetilsilano derivado del 3-buten-1-ol. De esta manera se obtienen únicamente el isómero *cis*, pero como una mezcla de diastereoisómeros en la posición exocíclica (**IV**).¹⁵ La síntesis prosigue con la desprotección del alcohol primario y formación del bromuro. La ruptura oxidativa del doble enlace y posterior oxidación del aldehído permite aislar finalmente el correspondiente metil éster **V**. A continuación se introduce la cadena lateral derivada del ácido hidroferúlico mediante un acoplamiento con EDC, una vez eliminado el grupo TBDPS. Los últimos pasos de la síntesis incluyen la desprotección de la amina con $\text{BF}_3 \cdot \text{OEt}_2$, ciclación de la misma e hidrogenación catalítica para obtener como producto mayoritario la amforoginina A y como producto minoritario su epímero en la posición 1 del anillo de pirrolizidina.

De esta manera el grupo de Yoda completó la síntesis de la amforoginina A en 21 pasos partiendo del ácido D-málico y con un rendimiento global del 5.1%.

¹⁴ H. Yoda, T. Egawa, K. Takabe, *Tetrahedron Lett.* **2003**, *44*, 1643-1646.

¹⁵ Se obtiene el producto con un exceso diastereomérico del 55% que se debe a que el aliltrimetilsilano empleado es una mezcla de isómeros geométricos *E/Z* (3.1/1.0).



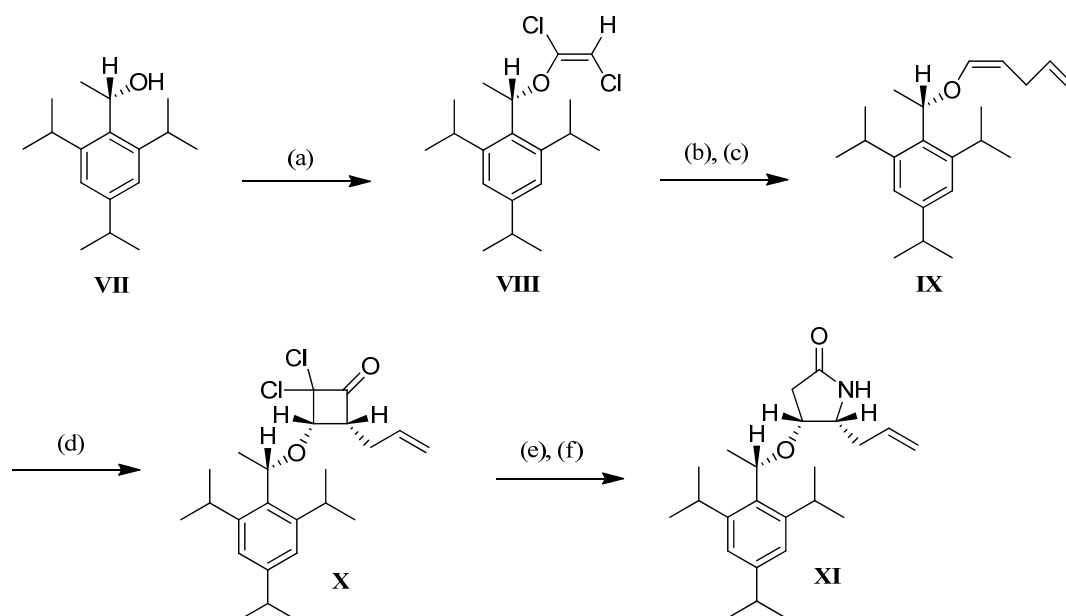
(a) i) NaBH_4 , MeOH, 0°C ; ii) $\text{BF}_3 \cdot \text{OEt}_2$, Et_3SiH , 0°C (69%, 2 etapas); iii) K_2CO_3 , MeOH; iv) BnBr , Ag_2O , DMF (92%). (b) i) CAN, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (9:1) (93%); ii) $(\text{Boc})_2\text{O}$, DMAP, Et_3N , CH_2Cl_2 , 0°C (cuant.); iii) Pd, HCOOH -MeOH, 45°C (cuant.); iv) TBDPSCl , imidazol, CH_2Cl_2 (94%). (c) i) NaBH_4 , MeOH, 0°C ; ii) $\text{MPMO}(\text{CH}_2)_2\text{CH}=\text{CHCH}_2\text{SiMe}_3$, $\text{BF}_3 \cdot \text{OEt}_3$, CH_2Cl_2 , -78°C (47%). (d) i) DDQ, $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (11:1), 0°C (90%); ii) CBr_4 , PPh_3 , CH_2Cl_2 (96%). (e) OsO_4 , NMO, acetona/ H_2O ; ii) NaIO_4 , eter/ $\text{THF}/\text{H}_2\text{O}$ (88%, 2 etapas); iii) Br_2 , NaHCO_3 , MeOH/ H_2O (9:1) (89%). (f) i) TBAF, THF, 0°C (87%); ii) ácido 3-(*p*-benciloxi-*m*-metoxifenil)propanoico, EDC, DMAP, CH_2Cl_2 , 0°C (70%). (g) $\text{BF}_3 \cdot \text{OEt}_3$, CH_2Cl_2 , -15°C ; ii) NaHCO_3 , H_2O (85%, 2 etapas). (h) H_2 , Pd/C, CH_3COOEt .

Esquema 4.1 Síntesis de la amforoginina A (Yoda, 2003).¹⁴

Ese mismo año aunque unos meses más tarde el grupo de Delair y Greene en Francia publicó también la síntesis de la amforoginina A.¹⁶ En este caso la aproximación es muy diferente ya que la etapa clave es una cicloadición [2+2] de una diclorocetena con un enol éter quiral, una reacción que ya había sido empleada por este mismo grupo para la síntesis de indolizidinas.¹⁷ La síntesis de este grupo parte del auxiliar quiral **VII** que es transformado en el dicloroenol éter **VIII** (Esquema 4.2). El tratamiento del mismo con *n*-BuLi y yoduro de alilo permite obtener el correspondiente inol éter que debido a su inestabilidad es hidrogenado al enol éter **IX**. El siguiente paso es la cicloadición diastereoselectiva de dicho enol éter con una diclorocetena generada en el medio de reacción. La síntesis prosigue con la expansión del anillo, vía transposición de Beckmann, y la eliminación de los dos átomos de cloro para dar la lactama **XI**.

¹⁶ C. Roche, P. Delair, A. Greene, *Org. Lett.* **2003**, 5, 1741-1744.

¹⁷ a) M. Pourashraf, P. Delair, M. O. Rasmussen, A. E. Greene, *J. Org. Chem.* **2000**, 65, 6966-6972; b) M. O. Rasmussen, P. Delair, A. E. Greene, *J. Org. Chem.* **2001**, 66, 5438-5443.

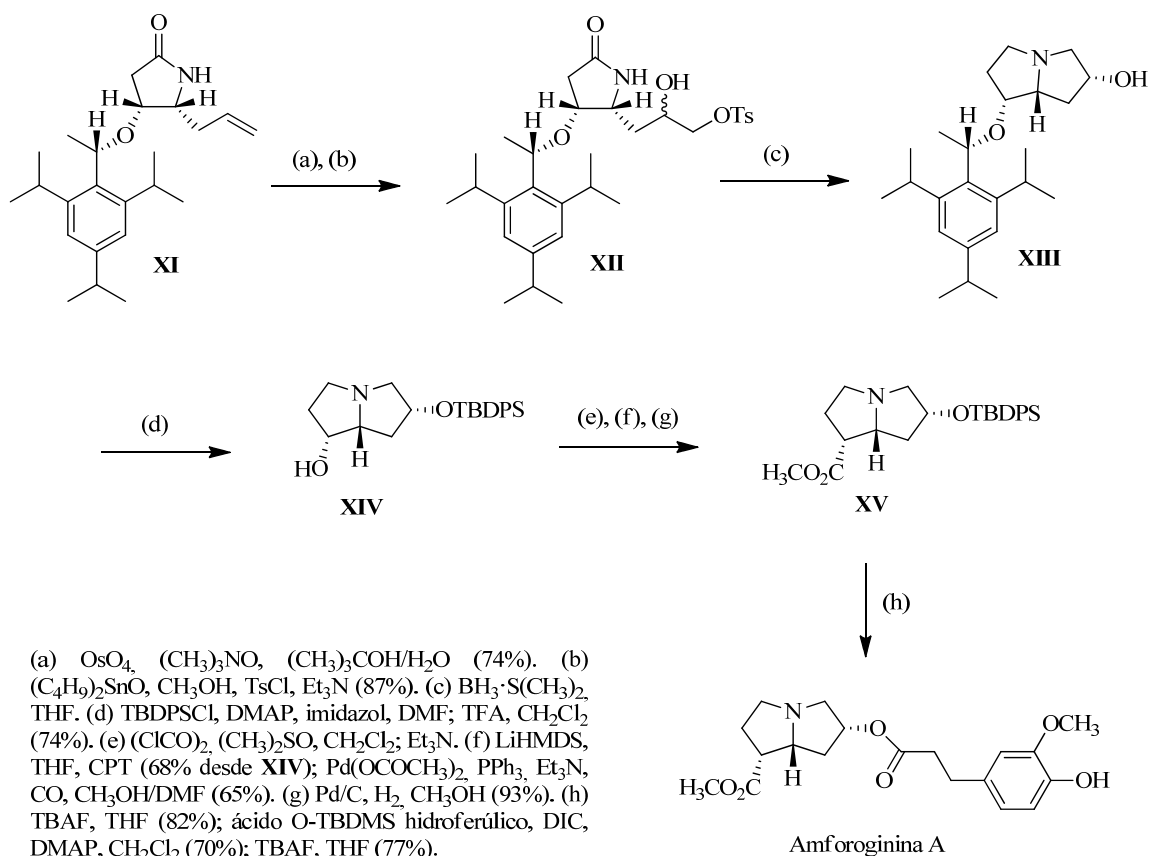


(a) KH, THF, $\text{Cl}_2\text{C}=\text{CHCl}$ (79%). (b) $n\text{-BuLi}$, HMPA, THF, $\text{CH}_2=\text{CHCH}_2\text{I}$. (c) Pd/BaSO_4 , H_2 , piridina, 1-hexeno. (d) Cl_3CCOCl , Zn-Cu, Et_2O . (e) $\text{NH}_2\text{OSO}_2\text{C}_6\text{H}_2(\text{CH}_3)_3$, CH_2Cl_2 . (f) Zn-Cu, NH_4Cl , CH_3OH (42% desde **VIII**).

Esquema 4.2. Síntesis de la amforoginina A (Delair y Greene, 2003).¹⁶

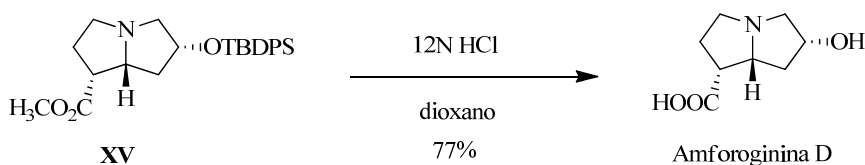
A continuación se lleva a cabo la dihidroxilación del doble enlace y la monotosilación selectiva para obtener el producto **XII** como mezcla de epímeros (Esquema 4.3). La reducción y ciclación de dicho intermedio conduce a la formación del anillo de pirrolizidina como una mezcla de epímeros en el hidroxilo en posición 6¹⁸ que es protegido con cloruro de *tert*-butildifenilsilano. Posteriormente se elimina el auxiliar quiral y se oxida el alcohol bajo las condiciones de Swern. La cetona obtenida es inestable y se lleva a cabo directamente una carbometoxilación, seguida de hidrogenación del doble enlace para obtener el compuesto **XV**. La síntesis concluye con la desprotección del alcohol, acoplamiento con el derivado del ácido hidroferúlico y final desprotección del fenol. De esta manera se sintetiza la amforoginina A en 17 etapas con un rendimiento global del 2.9%.

¹⁸ El isómero no deseado fue oxidado y reducido de nuevo para obtener finalmente un rendimiento del 50% del producto deseado con la estereoquímica correcta.



Esquema 4.3. Continuación de la síntesis de la amforoginina A (Delair y Green, **2003**).¹⁶

Posteriormente, en 2005, este mismo grupo publicó la síntesis de la amforoginina D.¹⁹ Esta última pudo ser sintetizada desde el compuesto **XV**, un intermedio de la síntesis de la amforoginina A, mediante una hidrólisis ácida y cromatografía de intercambio catiónico (Esquema 4.4).



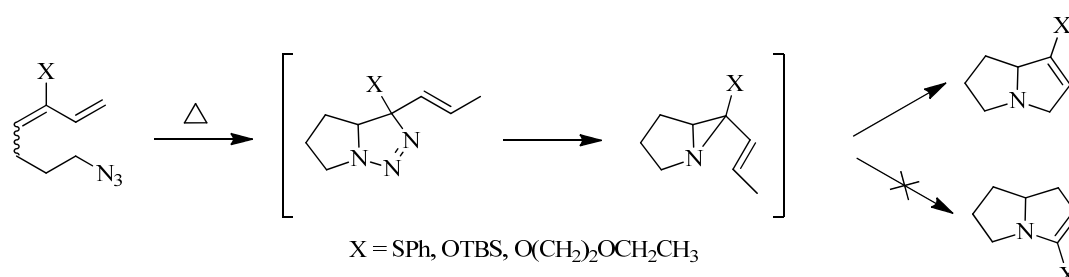
Esquema 4.4. Síntesis de la amforoginina D (Delair y Greene, **2005**).¹⁹

¹⁹ C. Roche, K. Kadlecikova, A. Veyron, P. Delair, C. Philouze, A. E. Greene, *J. Org. Chem.* **2005**, *70*, 8352-8363.

4.2.2.- Antecedentes en el empleo de la reacción de cicloadición 1,3-dipolar azida-alqueno intramolecular en la síntesis total de productos naturales.

Desde hace muchos años los alcaloides de pirrolizidina han suscitado el interés de los químicos orgánicos y se han descrito numerosas síntesis de muchos alcaloides de esta familia basadas en diferentes estrategias.²⁰ En nuestro caso, dada la experiencia del grupo en la reacción de cicloadición 1,3-dipolar azida-alqueno intramolecular, se ha completado la primera síntesis de la amforoginina C empleando esta reacción como etapa clave para formar uno de los anillos del esqueleto de pirrolizidina. Ya en el capítulo 2 se comentó el gran uso que se ha dado a esta reacción en química orgánica y en concreto se pueden encontrar en la literatura numerosos ejemplos de la utilización de esta reacción en la síntesis total de productos naturales y sus derivados.²¹ A continuación se citarán y comentarán algunos de los más relevantes.

En primer lugar cabe destacar una metodología desarrollada simultáneamente, de manera independiente por Pearson y Hudlicky en la que se sintetizan derivados de pirrolizidina mediante una cicloadición 1,3-dipolar de azidas con dienos.²² El grupo de Pearson emplea dienos heterosustituídos para controlar la regioquímica de la reacción (Esquema 4.5).



Esquema 4.5. Síntesis de pirrolizidinas de Pearson.

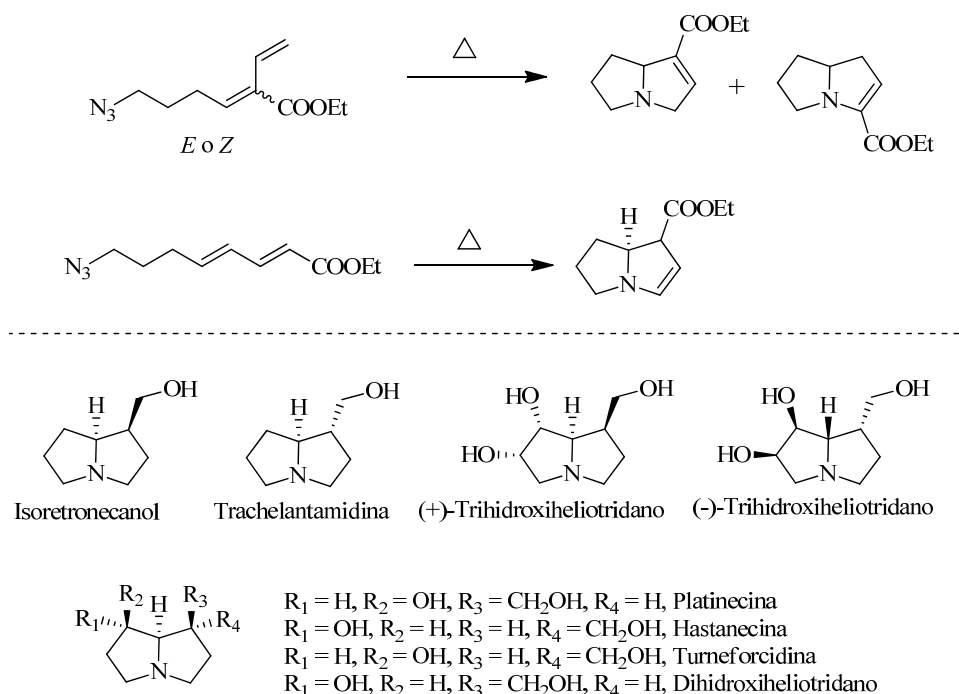
Simultáneamente, Hudlicky investigó la misma reacción. En este caso el dieno se encuentra activado por un éster y según sea la posición del mismo se pueden obtener los anillos de pirrolizidina con diferente sustitución (Esquema 4.6). Basándose en esta metodología el

²⁰ Para revisiones sobre la síntesis de alcaloides de pirrolizidina ver: a) W. M. Dai, Y. Nagao, *Heterocycles*, **1990**, 30, 1231-1261; b) D. J. Robins, *Nat. Prod. Rep.* **1995**, 12, 413-418; c) J. R. Liddell, *Nat. Prod. Rep.* **1996**, 13, 187-193; d) J. R. Liddell *Nat. Prod. Rep.* **1999**, 16, 499-507; e) J. R. Liddell *Nat. Prod. Rep.* **2002**, 19, 773-781.

²¹ a) Padwa, A. en *Synthetic applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* John Wiley & Sons, **2002**; b) V. Nair, T. D. Suja, *Tetrahedron*, **2007**, 63, 12247-12275.

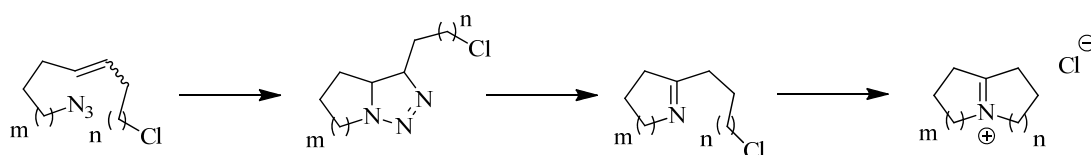
²² a) W. H. Pearson, *Tetrahedron Lett.* **1985**, 26, 3527-3530; b) T. Hudlicky, J. O. Frazier, G. Seoane, M. Tiedje, A. Seoane, L. D. Kwart, C. Beal, *J. Am. Chem. Soc.* **1986**, 108, 3755-3762; c) W. H. Pearson, J. E. Celebuski, Y.-F. Poon, B. R. Dixon, J. H. Glans, *Tetrahedron Lett.* **1986**, 27, 6301-6304; d) T. Hudlicky, G. Seoane, T. C. Lovelace, *J. Org. Chem.* **1988**, 53, 2094-2099; e) W. H. Pearson, S. C. Bergmeier, S. Degan, K. C. Lin, Y. F. Poon, J. M. Schkeryantz, J. P. Williams, *J. Org. Chem.* **1990**, 55, 5719-5738; f) T. Hudlicky, H. Luna, J. D. Price, F. Rulin, *J. Org. Chem.* **1990**, 55, 4683-4687; g) T. Hudlicky, G. Seoane, J. D. Price, K. G. Gadamasetti, *Synlett*, **1990**, 8, 433-440.

grupo de Hudlicky fue capaz de sintetizar formalmente varios alcaloides de este tipo como el isoretronecanol, la trachelantamidina, los dos enantiómeros del trihidroxiheliotridano, la platinecina, la hastanecina, la turneforcidina o el dihidroxiheliotridano.



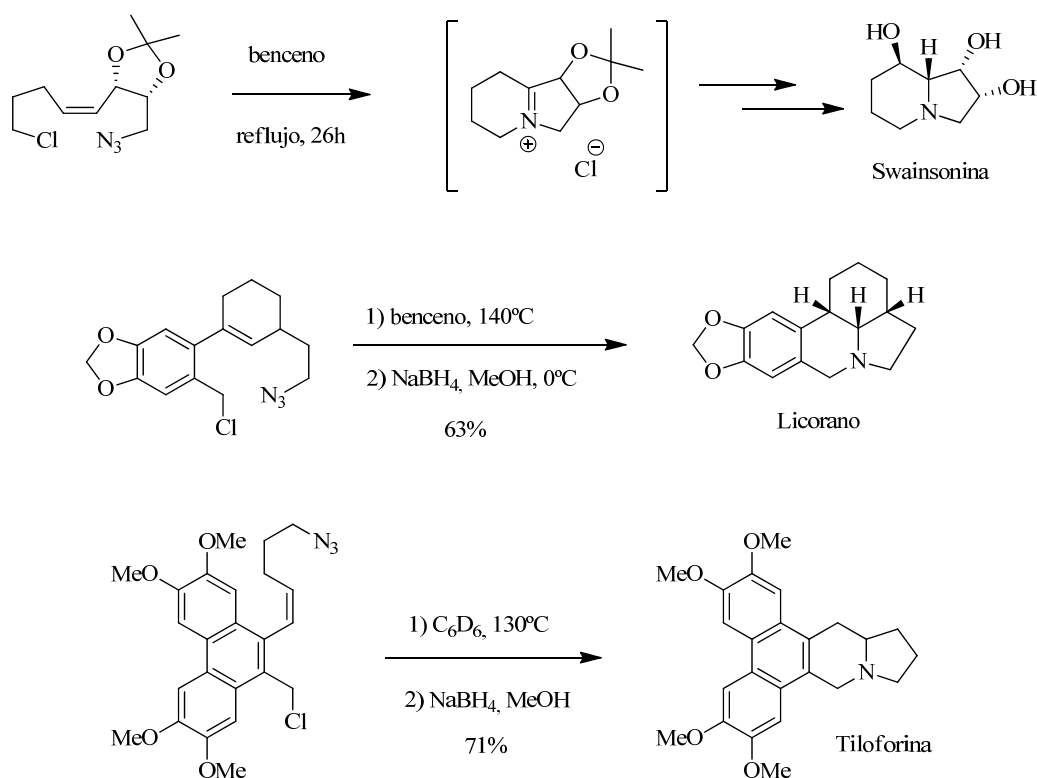
Esquema 4.6. Síntesis de pirrolizidinas de Hudlicky.

Además de la reacción de cicloadición de azidas con dienos, Pearson desarrolló también otra metodología para la formación de sistemas bicíclicos nitrogenados en un sólo paso basada en la reacción de azidas con ω -cloro alquenos (Esquema 4.7). En este proceso primero tiene lugar la cicloadición 1,3-dipolar azida-alqueno intramolecular para formar una triazolina que descompone eliminando nitrógeno y generando la correspondiente imina, la cual es *N*-alquilada obteniéndose así un ion iminio sobre el cual se pueden realizar diferentes transformaciones.



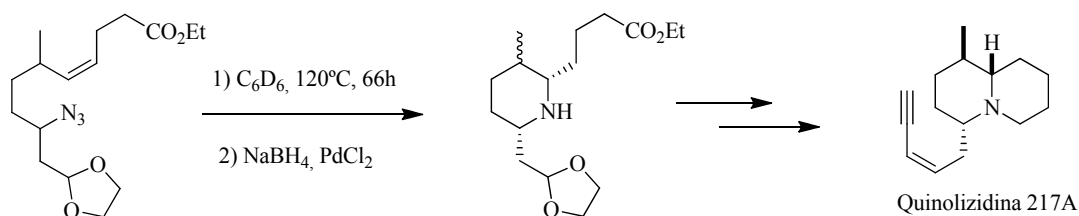
Esquema 4.7. Reacción de azidas con ω -cloro alquenos desarrollada por Pearson para la síntesis de sistemas bicíclicos nitrogenados.

Sirviéndose de esta reacción en cascada como etapa clave, Pearson completó las síntesis de la swainsonina,²³ el licorano²⁴ y la tiloforina²⁵ (Esquema 4.8).



Esquema 4.8. Síntesis de la swainsonina, el licorano y la tiloforina de Pearson.^{23, 24, 25}

También Pearson publicó unos años más tarde la síntesis de la quinolizidina 217A,²⁶ en la que volvió a valerse de una reacción de cicloadición 1,3-dipolar azida-alqueno intramolecular para la formación de unos de los anillos de la quinolizidina (Esquema 4.9). En este caso la imina obtenida es reducida directamente a la piperidina correspondiente como una mezcla de diastereoisómeros que luego pueden ser separados en una etapa posterior.



Esquema 4.9. Síntesis de la quinolizidina 217A de Pearson.²⁶

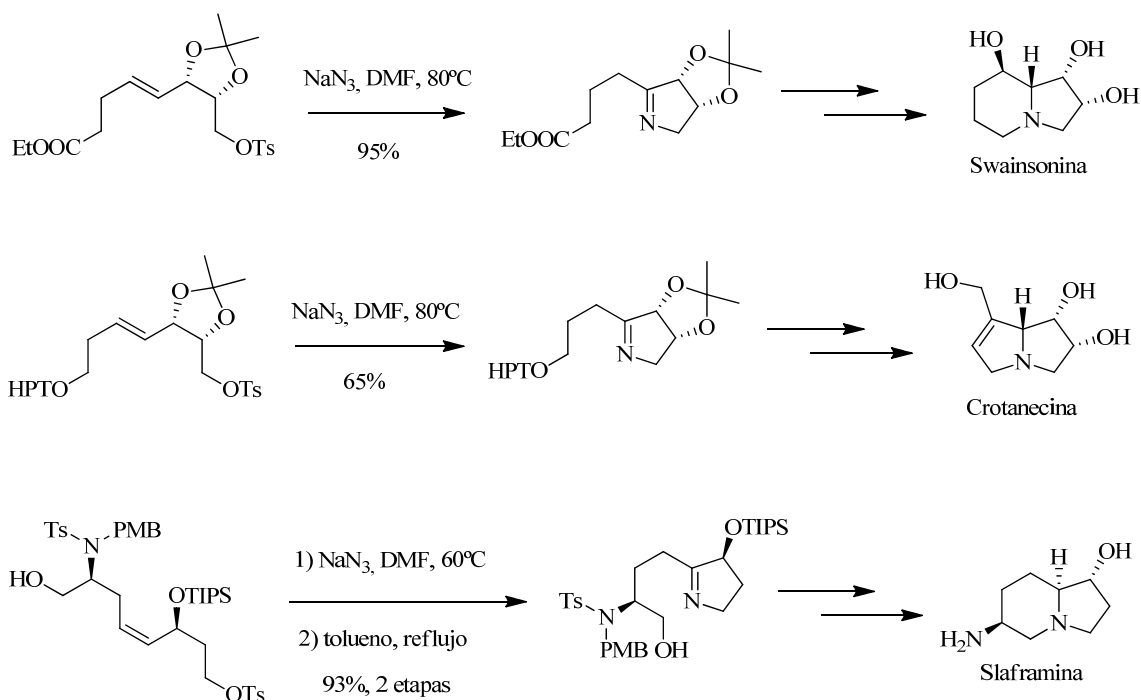
²³ W. H. Pearson, K.-C. Lin, *Tetrahedron Lett.* **1990**, 31, 7571-7574.

²⁴ W. H. Pearson, J. M. Schkeryantz, *J. Org. Chem.* **1992**, 57, 6783-6789.

²⁵ W. H. Pearson, R. Walavalkar, *Tetrahedron*, **1994**, 50, 12293-12304.

²⁶ W. H. Pearson, H. Suga, *J. Org. Chem.* **1998**, 63, 9910-9918.

Por otro lado el grupo de Cha publicó las síntesis de la swainsonina,²⁷ la crotanecina²⁸ y la slaframina.²⁹ En todas ellas se lleva a cabo una reacción de sustitución nucleófila de un tosilato con azida sódica, seguida de la reacción de cicloadición 1,3-dipolar azida-alqueno intramolecular para generar la correspondiente 1-pirrolina que dará lugar al anillo de cinco miembros del núcleo de indolizidina o pirrolizidina respectivamente (Esquema 4.10).



Esquema 4.10. Síntesis de la swainsonina, la crotanecina y la slaframina de Cha.^{27, 28, 29}

Otro ejemplo del empleo de esta reacción en la síntesis total de productos naturales lo encontramos en el grupo de Kim que publicó la síntesis de la antofina y la criptopleurina,³⁰ dos fenantroindolizidinas de la misma familia que la tiloforina sintetizada por Pearson (Esquema 4.11). En este caso se describe la formación de una mezcla de imina y aziridina³¹ como producto de la cicloadición, pero ambos productos se hidrogenan para obtener la correspondiente amina cíclica.

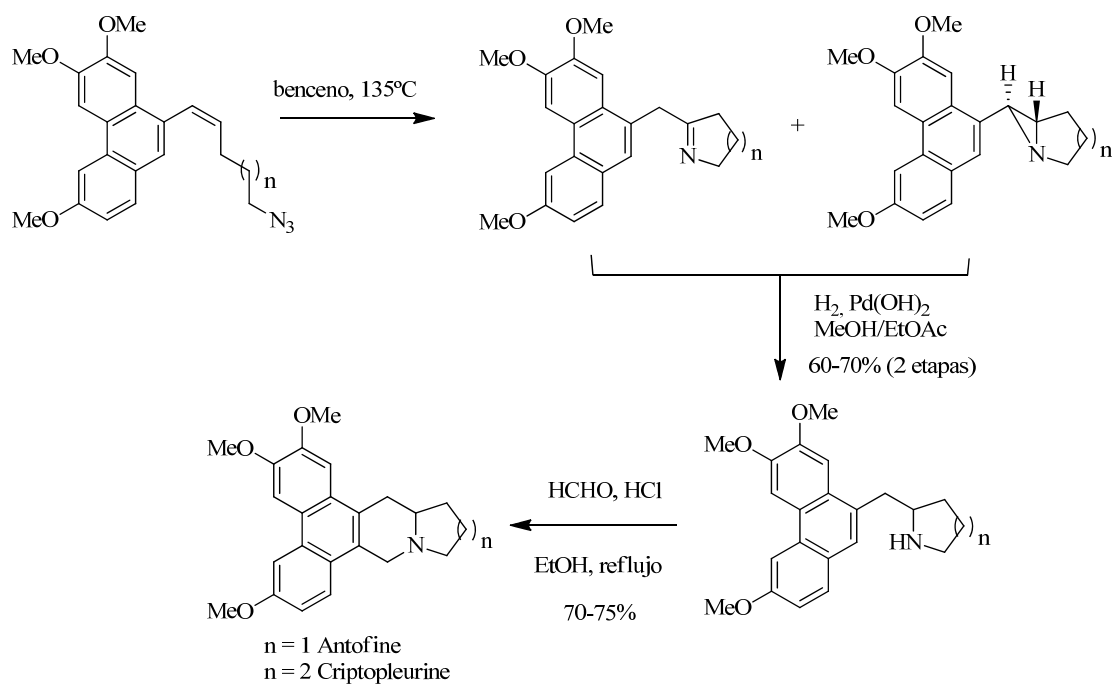
²⁷ R. B. Bennett III; J. R. Choi, W. D. Montgomery, J. K. Cha, *J. Am. Chem. Soc.* **1989**, *111*, 2580-2582.

²⁸ R. B. Bennett III, J. K. Cha, *Tetrahedron Lett.* **1990**, *31*, 5437-5440.

²⁹ J.-R. Choi, S. Han, J. K. Cha, *Tetrahedron Lett.* **1991**, *32*, 6469-6472.

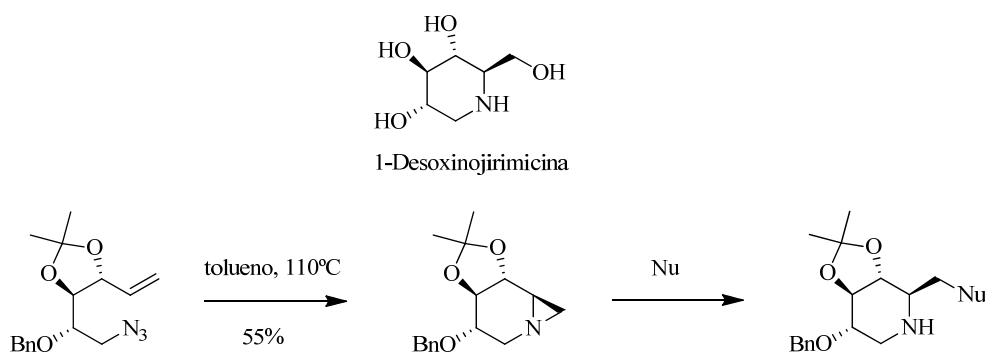
³⁰ S. Kim, Y. M. Lee, J. Lee, T. Lee, Y. Fu, Y. Song, J. Cho, D. Kim, *J. Org. Chem.* **2007**, *72*, 4886-4891.

³¹ Los autores describen la obtención de la misma proporción de imina y aziridina (2,2:1) empleando benceno a reflujo o un tubo sellado a 135°C. Además estudian la influencia de la geometría del doble enlace y preparan el isómero *trans* que conduce al mismo resultado. Finalmente para comprobar si la imina es un producto de la conversión de la aziridina, calientan esta última en las mismas condiciones de reacción, pero sólo obtienen después de 24 horas menos de un 5% de conversión y varios productos fruto de la descomposición de la aziridina.



Esquema 4.11. Síntesis de la antofina y la criptopleurina de Kim.³⁰

También encontramos el empleo de esta reacción para la síntesis de derivados de la 1-desoxinojirimicina, un potente inhibidor de glicosidasas cuyos derivados han encontrado aplicación en el tratamiento del VIH o la hepatitis C.³² En 2008 Murphy publicó una sencilla ruta de síntesis de derivados de este compuesto en la que se lleva a cabo una cicloadición 1,3-dipolar azida-alqueno con un doble enlace terminal para formar una aziridina la cual se hace reaccionar con diferentes nucleófilos accediendo así a diferentes derivados de la 1-desoxinojirimicina³³ (Esquema 4.12). De este modo se pueden obtener de manera muy sencilla y directa muchas estructuras relacionadas con este interesante producto natural.



Esquema 4.12. Síntesis de derivados de la 1-desoxinojirimicina.³³

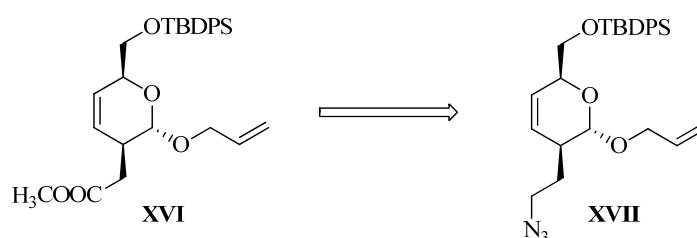
³² a) B. Winchester, G. W. J. Fleet, *Glycobiology*, **1992**, 2, 199-210; b) A. B. Hughes, A. J. Rudge, *Nat. Prod. Rep.* **1994**, 11, 135-162.

³³ Y. Zhou, P. V. Murphy, *Org. Lett.* **2008**, 10, 3777-3780.

4.3.- EXPOSICIÓN DE RESULTADOS.

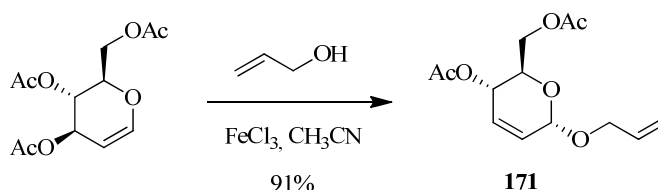
4.3.1.- Síntesis del derivado de hexahidropirano[4,3-b]pirrol mediante cicloadición 1,3-dipolar azida-alqueno intramolecular.

Desde hace años en nuestro grupo de investigación se ha trabajado en el campo de los carbohidratos y sus derivados.³⁴ Fue por eso que nos propusimos estudiar la reacción de cicloadición 1,3-dipolar azida-alqueno intramolecular en un derivado de carbohidrato.³⁵ Para ello se decidió preparar el azido alqueno **XVII** a partir de compuesto **XVI** cuya preparación fue descrita anteriormente por nuestro grupo,^{34c} y que pensamos nos permitiría acceder al azido alqueno realizando transformaciones sencillas sobre el éster metílico (Esquema 4.13).



Esquema 4.13. Esquema retrosintético del azido alqueno.

En primer lugar se describirá la síntesis del éster metílico **XVI** que se llevó a cabo siguiendo el procedimiento puesto a punto anteriormente en el grupo. Partiendo del tri-*O*-acetil-*D*-glucal se llevó a cabo una reacción de Ferrier³⁶ con alcohol alílico catalizada por tricloruro de hierro³⁷ para obtener el producto **171** como una mezcla de anómeros $\alpha:\beta$ en proporción 8:1 (Esquema 4.14). En este punto ambos compuestos resultaron difíciles de separar y se prosiguió la síntesis con la mezcla de ambos.



Esquema 4.14. Síntesis del diacetato **171**.

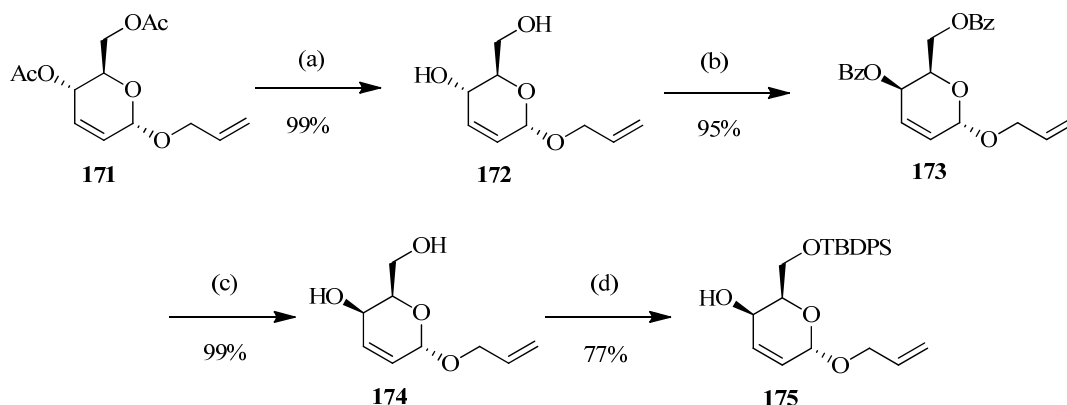
³⁴ a) A. Montero, E. Mann, B. Herradón, *Eur. J. Org. Chem.* **2004**, 3063-3073; b) A. Montero, E. Mann, B. Herradón, *Tetrahedron Lett.* **2005**, 46, 401-405; c) A. Montero, E. Benito, B. Herradón, *Tetrahedron Lett.* **2010**, 51, 277-280.

³⁵ Para algunos ejemplos de cicloadición 1,3 dipolar azida-alqueno intramolecular en derivados de carbohidratos ver: a) Y. Konda, T. Sato, K. Tsushima, M. Dodo, A. Kusunoki, M. Sakayanagi, N. Sato, K. Takeda, Y. Hiragaya, *Tetrahedron*, **1999**, 55, 12723-12740; b) Y. Konda-Yamada, K. Asano, t. Satou, S. Monma, M. Sakayanagi, N. Satou, K. Takeda, Y. Harigaya, *Chem. Pharm. Bull.* **2005**, 53, 529-536.

³⁶ a) R. J. Ferrier, *Topics Curr. Chem.* **2001**, 215, 153-175; b) R. J. Ferrier, O. A. Zubkov, *Org. React.* **2003**, 62, 569-736.

³⁷ C. Masson, J. Soto, M. Bessodes, *Synlett*, **2000**, 9, 1281-1282.

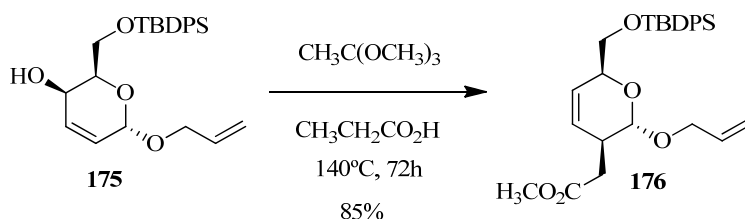
La metanolisis de dicha mezcla condujo con rendimiento cuantitativo al diol **172** sobre el cual se llevó a cabo una reacción de Mitsunobu³⁸ obteniéndose el dibenzoato **173** con configuración relativa *cis* en las posiciones 2 y 3 del anillo de pirano (Esquema 4.15). La hidrólisis básica de este intermedio empleando metóxido sódico en metanol permitió obtener el diol **174** el cual fue protegido selectivamente en el alcohol primario con cloruro de *tert*-butildifenilsilano. En este punto se pudo separar el anómero minoritario y proseguir la síntesis con el producto **175** isoméricamente puro.



(a) KOH/MeOH; (b) Ph₃P, DIAD, PhCOOH, THF; (c) MeONa/MeOH; (d) TBDPS-Cl, Et₃N, DMAP, CH₂Cl₂

Esquema 4.15. Síntesis del alcohol **175**.

La transposición de Claisen-Johnson³⁹ se llevó a cabo mediante reflujo del alcohol alílico **175** en trimetilortoacetato en presencia de ácido propanoico, obteniéndose de esta manera el éster metílico **176** de manera totalmente estereoselectiva y con buen rendimiento (Esquema 4.16).⁴⁰



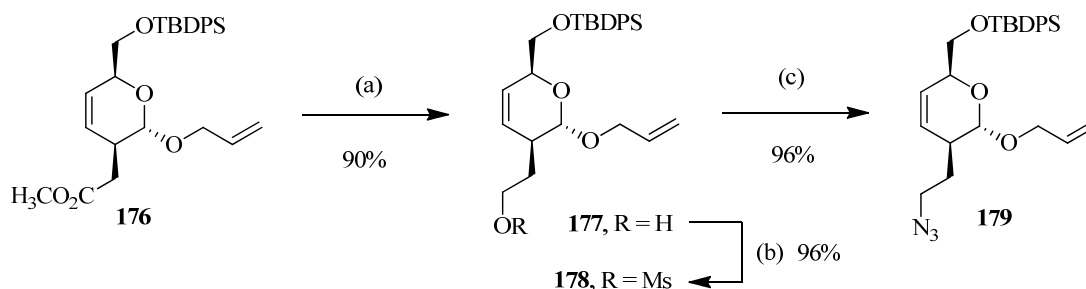
Esquema 4.16. Transposición de Claisen-Johnson del alcohol alílico **176**.

³⁸ a) O. Mitsunobu, *Synthesis*, **1981**, 1, 1-28; b) K. C. K. Swamy, N. N. B. Kumar, E. Balaraman, K. V. P. P. Kumar, *Chem. Rev.* **2009**, 109, 2551-2651.

³⁹ W. S. Johnson, L. Werthmann, W. R. Bartlett, T. J. Brockson, T.-T. Li, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.* **1970**, 92, 741-743.

⁴⁰ La estereoquímica del hidroxilo en posición 3 del anillo es fundamental para obtener una buena conversión y elevado rendimiento como ya se demostró en nuestro grupo anteriormente. De hecho en un trabajo del grupo de Krohn (K. Krohn, U. Flörke, D. Gehle, *J. Carbohydrate Chem.* **2002**, 21, 431-443) se describe una transposición de Claisen-Johnson en similares condiciones y con un sustrato parecido, pero epimérico en esta posición y la conversión desciende al 55%.

La reducción con borohidruro de litio del éster condujo al alcohol **177** que por tratamiento con cloruro de mesilo en presencia de trietilamina permitió obtener el correspondiente metanosulfonato **178** (Esquema 4.17). Por último se llevó a cabo una sustitución nucleófila con azida sódica en DMF para obtener el azido alqueno **179** deseado con muy buen rendimiento.

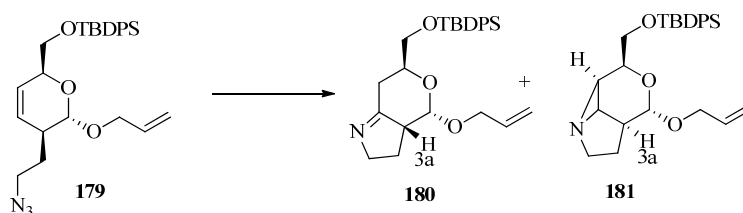


(a) LiBH_4 , THF, MeOH; (b) MsCl , Et_3N , CH_2Cl_2 ; (c) NaN_3 , DMF, 60°C , 2h

Esquema 4.17. Síntesis del azido alqueno **179**.

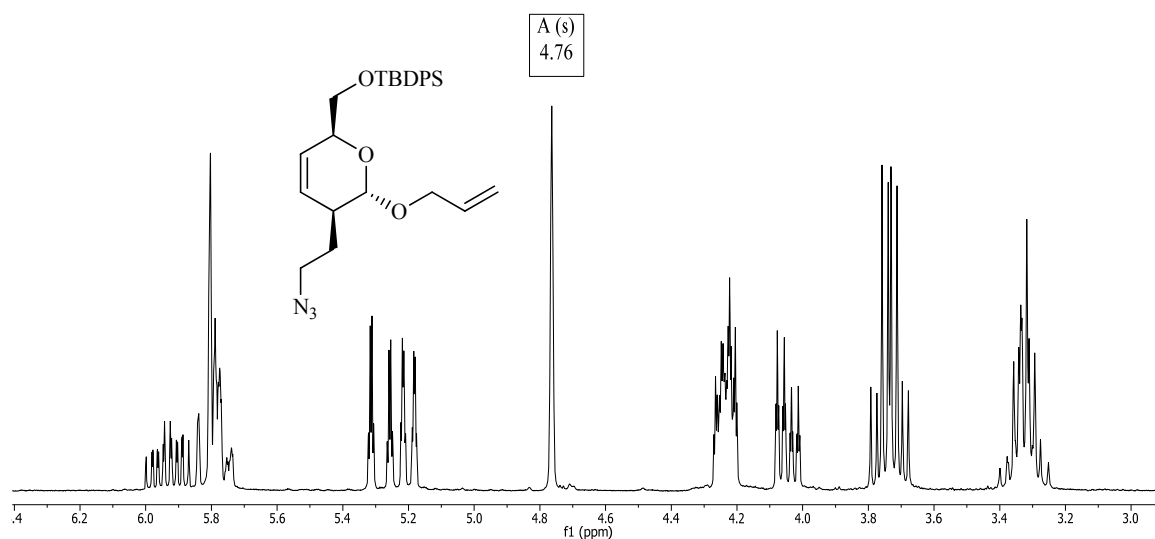
Una vez puesta a punto la ruta de síntesis para el azido alqueno propuesto, se comenzó a estudiar la reacción de cicloadición 1,3-dipolar, ensayándose diferentes condiciones de reacción con el fin de optimizar el proceso (Tabla 4.1). Se comparó el resultado de emplear DMF o tolueno como disolvente; así como el calentamiento con tubo sellado en un baño de silicona, o el calentamiento por radiación de microondas. En todos los casos se observó la formación de una mezcla de la imina **180** y la aziridina **181** en menor proporción. Los mejores resultados se lograron calentando a 140°C en tolueno con un tubo sellado durante 24 horas obteniéndose así la imina **180** con un 68% de rendimiento y la aziridina **181** con un 16% (entrada 2).

Como puede observarse en la estructura de la imina **180**, durante la reacción de cicloadición tiene lugar una completa epimerización en el carbono C-3a. Esta epimerización es posible gracias al equilibrio imina-enamina obteniéndose únicamente el producto termodinámicamente más estable. Por el contrario esta epimerización no se observa en la aziridina, ya que no es posible dicho equilibrio.

Tabla 4.1. Optimización de la reacción de cicloadición 1,3-dipolar azida-alqueno.

Entrada	Calentamiento	Disolvente	Temperatura	Tiempo	Rendimiento	
			[°C]		Imina	Aziridina
1	Tubo sellado	DMF	140	24	54	12
2	Tubo sellado	Tolueno	140	24	68	16
3	Microondas	DMF	140	3	43	10
4	Microondas	Tolueno	120	4	59	14

La confirmación de esta epimerización se obtuvo del estudio de los espectros de resonancia magnética nuclear. Es conocido que los 3,6-dihidro-2*H*-piranos sustituidos en posición 3 se caracterizan por una constante de acoplamiento $J_{2,3} \approx 0$ Hz para la disposición *trans*.⁴¹ Así en los compuestos con esta estereoquímica (la azida **179** y la aziridina **181**), la señal del protón en posición anomérica se observa como un singlete (Figuras 4.4 y 4.5). Sin embargo, en la imina **180** esta señal de protón aparece como un doblete con una constante de acoplamiento $J = 4.7$ Hz lo cual nos hizo sospechar de una posible epimerización en este carbono (Figura 4.6).

**Figura 4.4.** Espectro de ^1H -RMN del compuesto **179**.

⁴¹ a) R. J. Ferrier, N. Vethaviasar, *J. Chem. Soc. (C)*, **1971**, 1907-1913; b) R. J. Ferrier, N. Vethaviasar, *J. Chem. Soc. Perkin Trans. 1*, **1973**, 1791-1793.

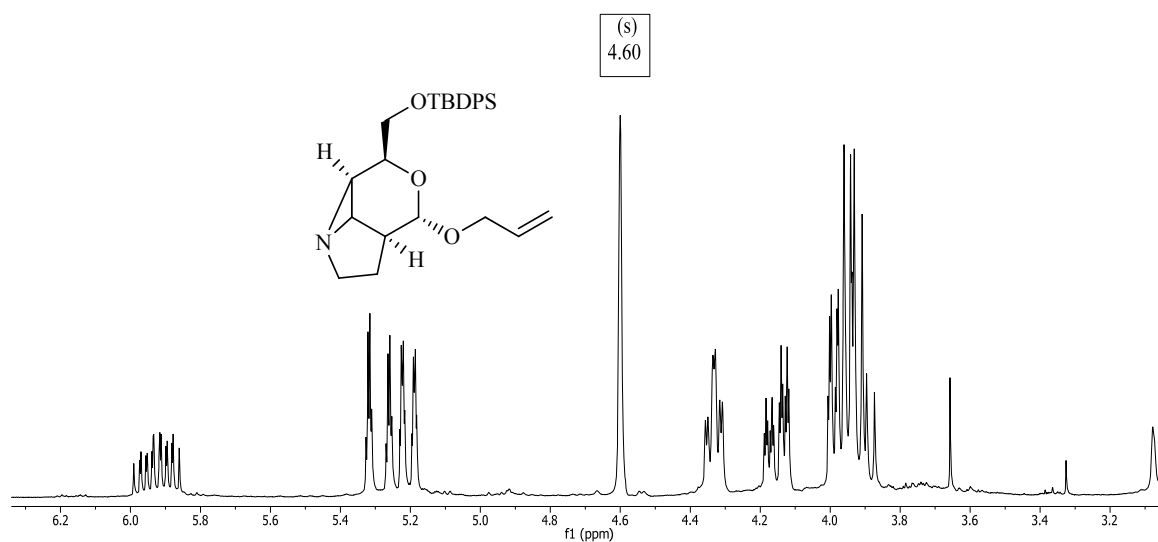


Figura 4.5. Espectro de ^1H -RMN del compuesto **181**.

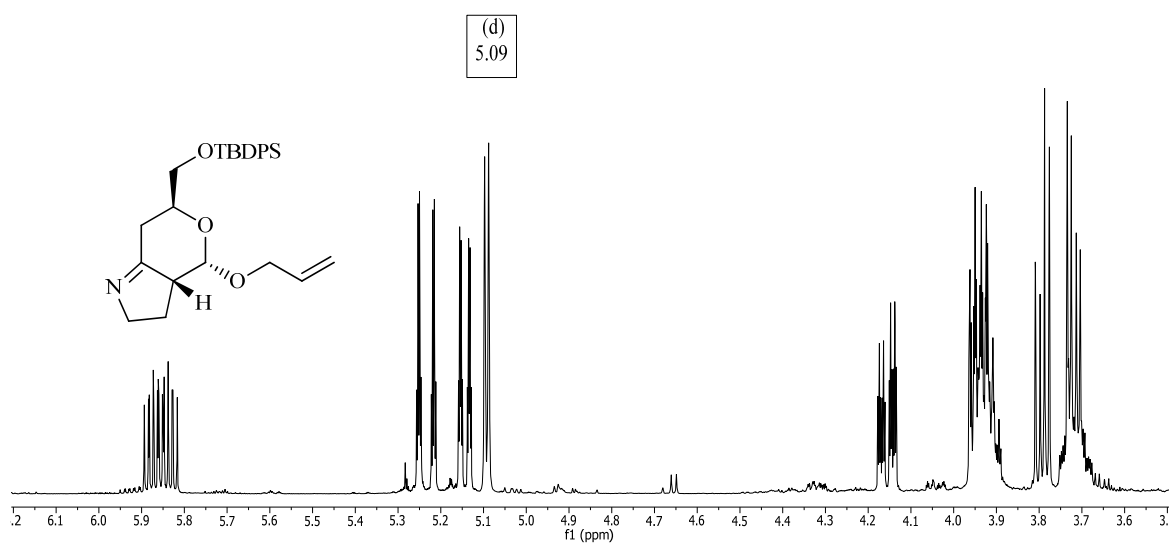


Figura 4.6. Espectro de ^1H -RMN del compuesto **180**.

Para comprobar esta inversión en la estereoquímica se realizó también un espectro NOESY del compuesto **180** (Figura 4.7). En él se observa el pico de cruce entre los protones H-3a (2.91 ppm) y H-4 (5.08 ppm).

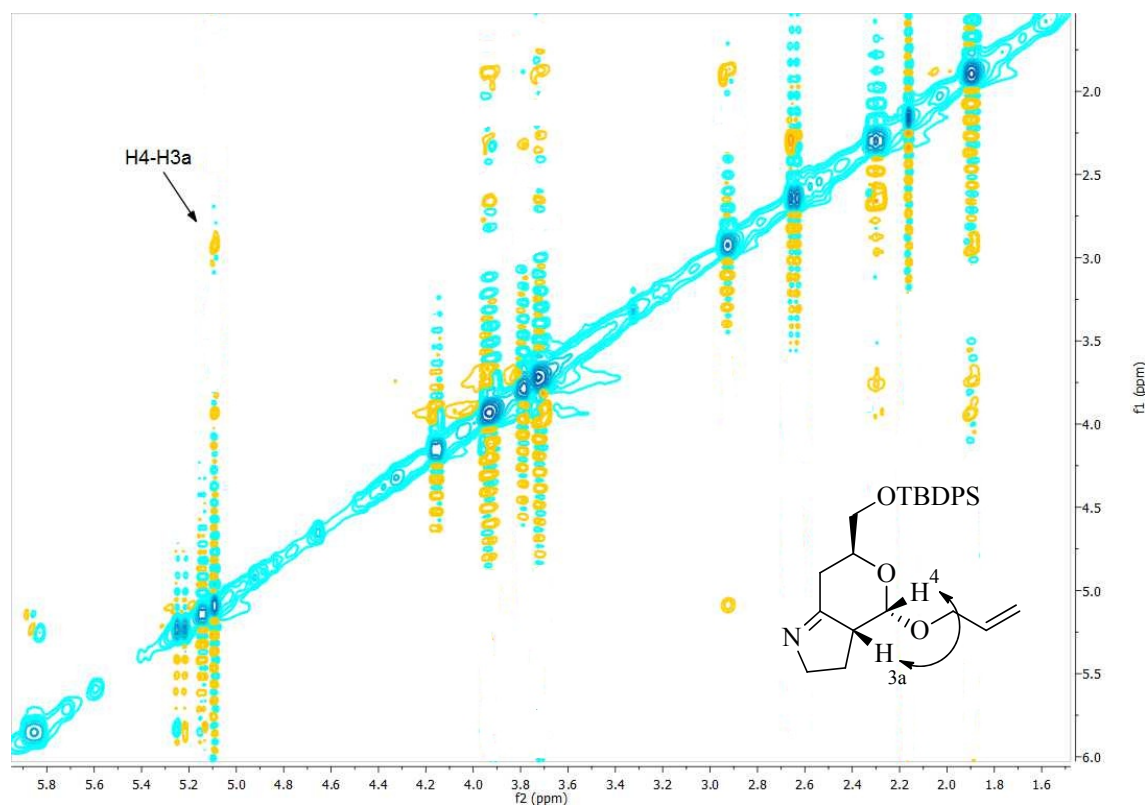
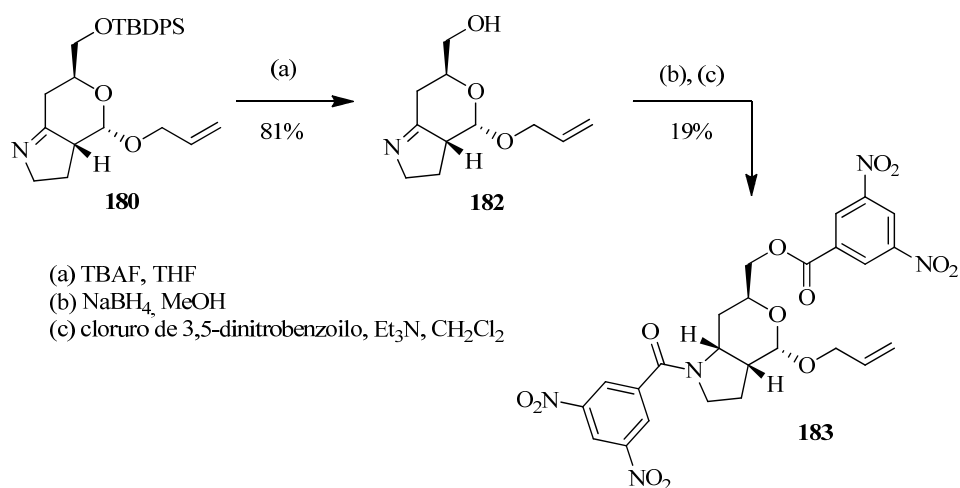
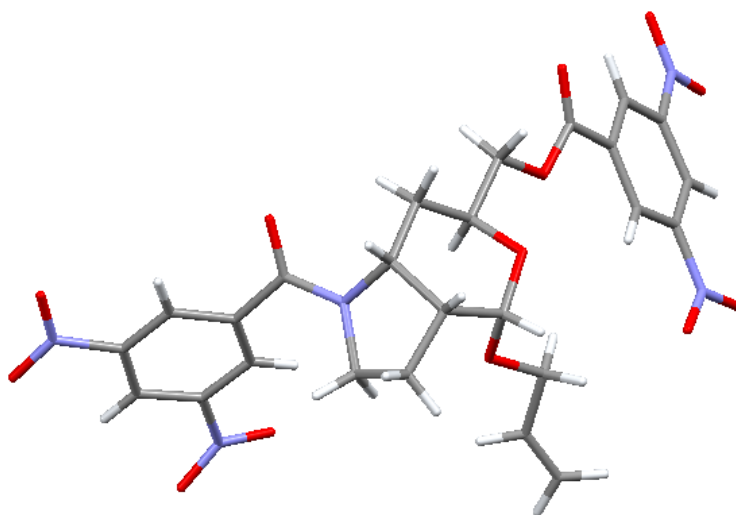


Figura 4.7. Espectro NOESY del compuesto **180**.

Por otro lado, con el objetivo de confirmar indudablemente la estereoquímica del compuesto se preparó un derivado con el que poder obtener cristales que permitiesen llevar a cabo un estudio por difracción de rayos X. Para ello se hizo reaccionar el compuesto **180** con TBAF obteniéndose el imino alcohol **182** que fue reducido con NaBH_4 y doblemente acilado con cloruro de 3,5-dinitrobenzoilo en presencia de trietilamina (Esquema 4.18). Se sintetizó así el producto **183** que cristalizó y permitió obtener la confirmación de la estereoquímica por difracción de rayos X (Figura 4.8).⁴²

⁴² Aunque la difracción de rayos X proporciona la configuración relativa, la absoluta se deduce de la ruta de síntesis.

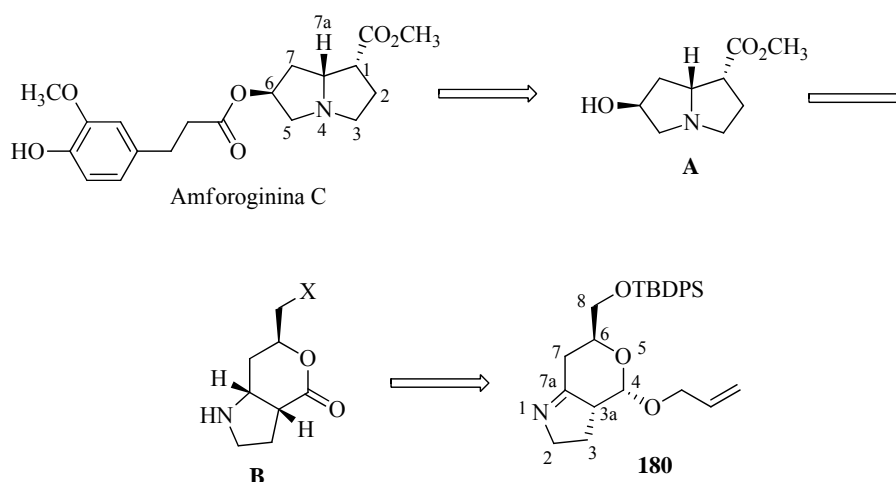
Esquema 4.18. Síntesis del compuesto **183**.Figura 4.8. Estructura de difracción de rayos X del compuesto **183**.⁴³

4.3.2.- Modificaciones sobre el derivado de hexahidropirano[4,3-b]pirrol para la síntesis de la amforoginina C.

Una vez obtenida la imina **180** y confirmada la inversión de la configuración en el carbono C-3a de la misma, observamos que en este compuesto están presentes todos los átomos de carbono y nitrógeno necesarios para formar el anillo de pirrolizidina de la amforoginina C con la estereoquímica adecuada en las posiciones C-3a y C-6 que se corresponderían con los

⁴³ Los datos de difracción de rayos X del compuesto **183** se encuentran en el anexo II.

carbonos C-1 y C-6 de la amforoginina C. Por ello nos planteamos la síntesis de este producto natural de acuerdo al esquema retrosintético que se muestra a continuación (Esquema 4.19).



Esquema 4.19. Esquema retrosintético de la amforoginina C.

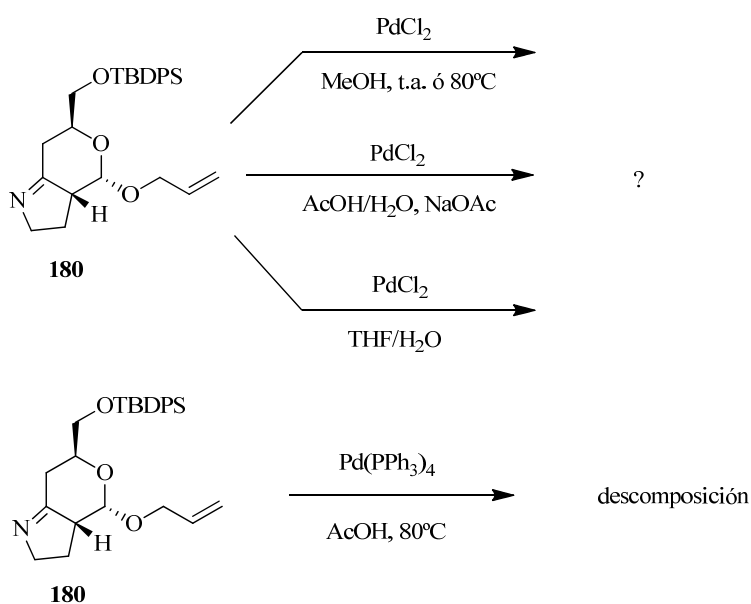
La amforoginina C se obtendría mediante esterificación del alcohol **A** con el ácido hidroferúlico. A su vez este sistema de 1-azabicyclo[3.3.0]octano se sintetizaría mediante apertura de la lactona **B** convenientemente funcionalizada, seguida de ciclación. Finalmente la lactona sería el producto de la oxidación en la posición anomérica y reducción estereoselectiva de la imina **180** ya preparada.

Decidimos por tanto comenzar con la eliminación del alilo para poder llevar a cabo después la oxidación en la posición anomérica del anillo de pirano. El grupo alilo es ampliamente empleado en síntesis orgánica como grupo protector especialmente en el campo de los carbohidratos,⁴⁴ ya que permite ser eliminado bajo condiciones suaves de reacción empleando complejos de paladio.⁴⁵ En primer lugar se hizo reaccionar el compuesto **180** con PdCl₂ en metanol a temperatura ambiente, pero no se observó la desprotección, incluso empleando el catalizador en cantidades estequiométricas (Esquema 4.20). El empleo de estas mismas condiciones de reacción, pero a 80°C tampoco condujo al producto deseado. En ambos casos sí se observó la desaparición del producto de partida y la formación de otro compuesto cuyo espectro de ¹H-RMN mostraba las señales del grupo alilo y el resto de protones de la imina de partida, aunque con desplazamientos químicos algo diferentes. Además se realizó un espectro de masa exacta y se comprobó que la masa no había variado. Sin embargo en base a estos datos estructurales no se consiguió dilucidar su estructura exacta. Se decidió por tanto emplear otros

⁴⁴ a) P. A. Manthorpe, R. Gigg, *Methods Carbohydr. Chem.* **1980**, 8, 305; b) P. Bloullanger, P. Chatelard, G. Descotes, M. Kloosterman, J. H. van Boom, *J. Carbohydr. Chem.* **1986**, 5, 541-559.

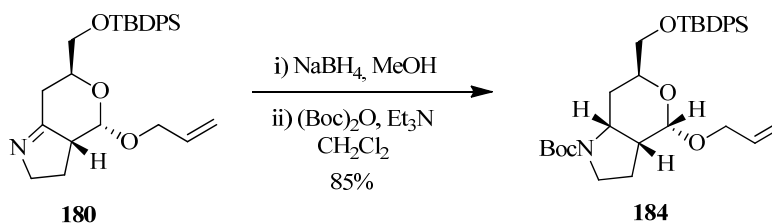
⁴⁵ F. Guibé, *Tetrahedron*, **1998**, 54, 2967-3042.

medios de reacción como fueron una mezcla de AcOH/H₂O, en presencia de NaOAc,⁴⁶ así como THF/H₂O (9:1), pero el resultado fue el mismo. Por otro lado el intento de emplear otro catalizador de paladio, Pd(PPh₃)₄ en AcOH a 80°C,⁴⁷ provocó la descomposición de la imina de partida. Con todo ello se pensó que el problema podía deberse a la interacción de la imina con el paladio y se decidió cambiar de estrategia y reducir la imina antes de llevar a cabo la desprotección.



Esquema 4.20. Intentos de eliminación del grupo alilo.

La reducción de la imina **180** se llevó a cabo con NaBH₄ en metanol, y la amina obtenida se protegió *in situ* por reacción con di-*tert*-butil dicarbonato y trietilamina en diclorometano (Esquema 4.21). Como era de esperar la reducción tiene lugar por la cara menos impedida del sistema bicíclico y se obtuvo el producto **184** como un único diastereoisómero y con un rendimiento del 85% para las dos etapas.



Esquema 4.21. Síntesis del compuesto **184**.

⁴⁶ a) F. A. Jaipuri, N. L. Pohl, *Org. Biomol. Chem.* **2008**, 6, 2686-2691; b) W. J. Morris, M. D. Shair, *Org. Lett.* **2009**, 11, 9-12.

⁴⁷ X. Zhu, B. Yu, Y. Hui, R. R. Schmidt, *Eur. J. Org. Chem.* **2004**, 965-973.

La configuración relativa *cis* de los hidrógenos en posiciones H-7a (3.99 ppm), H-3a (2.48 ppm) y H-4 (4.95ppm) fue además confirmada mediante un espectro NOESY del compuesto (Figura 4.9).

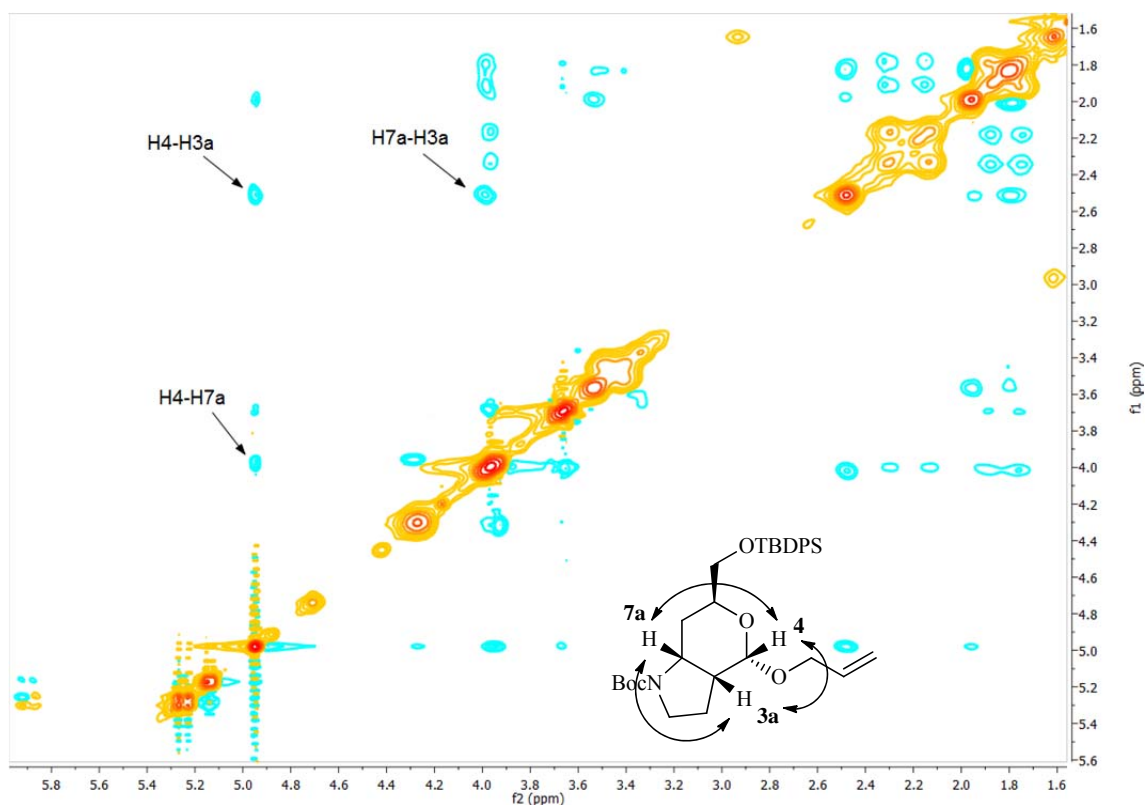
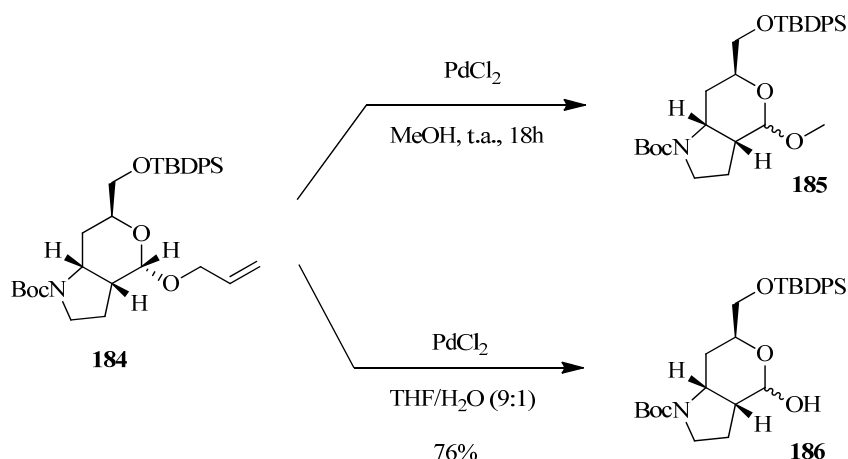


Figura 4.9. Espectro NOESY del compuesto **184**.

El siguiente objetivo fue de nuevo la eliminación del grupo alilo una vez reducida la imina. Para ello se hizo reaccionar el compuesto **184** con PdCl_2 en MeOH a temperatura ambiente durante toda una noche. Sin embargo, aunque se observó la desaparición de las señales del alilo en el espectro de ^1H -RMN, no se obtuvo el producto deseado sino el acetal **185** (Esquema 4.22). Esto puede deberse a la actuación del metanol como nucleófilo en la reacción y por tanto se decidió sustituir el disolvente. Se probó entonces con una mezcla de THF/ H_2O (9:1), obteniéndose en este caso el lactol **186** como mezcla de diastereoisómeros (85:15) que pudieron ser separados por cromatografía en columna para su caracterización.



Esquema 4.22. Síntesis del lactol 186.

Siguiendo con la estrategia planteada para la síntesis de la amforoginina C se procedió a oxidar la mezcla de los lactoles obtenidos. En primer lugar, se empleó el reactivo de Dess-Martin⁴⁸ que ha sido descrito anteriormente para la oxidación de lactoles a lactonas.⁴⁹ Sin embargo tras 24 horas de reacción se obtuvo el lactol inalterado (Esquema 4.23). A continuación se probó con PCC en diclorometano,⁵⁰ pero de nuevo se recuperó el producto de partida. Tras realizar de nuevo una búsqueda bibliográfica más exhaustiva de métodos para llevar a cabo esta oxidación se decidió emplear MnO_2 ,⁵¹ sin embargo el resultado fue el mismo. Igualmente de nuevo se recuperó el lactol al emplear perrutenato de tetrapropilamonio en combinación con *N*-óxido de *N*-metil morfolina.⁵²

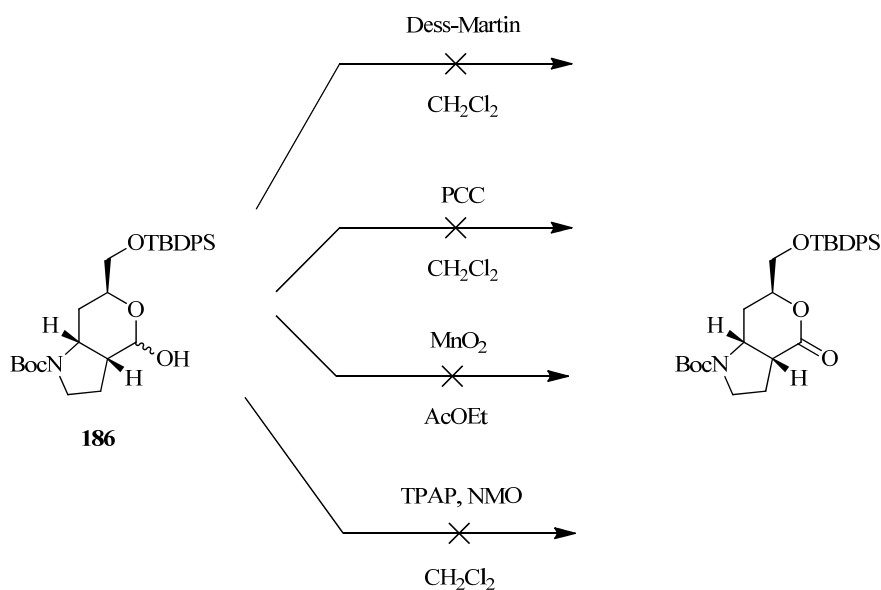
⁴⁸ a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155-4156; b) D. B. Dess, J. C. Martin. *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287.

⁴⁹ a) R. Csuk, P. Dörr, *J. Carbohydr. Chem.* **1995**, *14*, 35-44; b) J. S. Yadav, K. V. Rao, A. R. Prasad, *Synthesis*, **2006**, *22*, 3888-3894.

⁵⁰ Para algunos ejemplos de oxidación de lactoles a lactones con PCC ver: a) D. F. Tabber, P. B. Dekker, M. D. Gaul, *J. Am. Chem. Soc.* **1987**, *109*, 7488-7494; b) Y. Shi, W. D. Wulff, *J. Org. Chem.* **1994**, *59*, 5122-5124; c) E. Álvarez, R. Pérez, M. Rico, R. M. Rodríguez, J. D. Martín, *J. Org. Chem.* **1996**, *61*, 3003-3016; d) R. P. Smyj, J. M. Chong, *Org. Lett.* **2001**, *3*, 2903-2906.

⁵¹ a) J. M. Harris, G.A. O'Doherty, *Tetrahedron Lett.* **2000**, *41*, 183-187; b) J. Casas, M. Engqvist, I. Ibrahim, B. Kaynak, A. Córdova, *Angew. Chem. Int. Ed.* **2005**, *44*, 1343-1345.

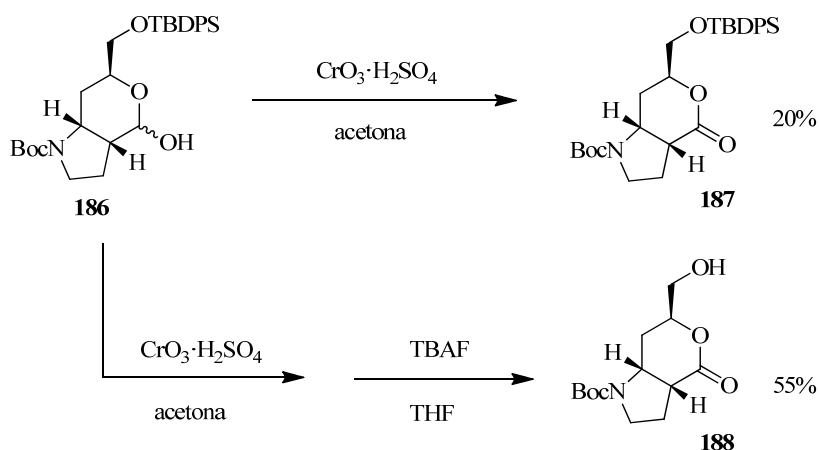
⁵² a) R. Benhaddou, S. Czernecki, W. Farid, G. Ville, J. Xie, A. Zegar, *Carbohydr. Res.* **1994**, *260*, 243-250; b) J. Derien, L. Ropartz, J. Le Paih, P. H. Dixneuf, *J. Org. Chem.* **1999**, *64*, 3524-3531.



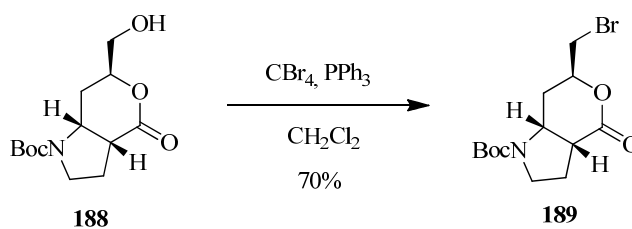
Esquema 4.23. Intentos de oxidación del lactol **186**.

Finalmente se llevó a cabo la oxidación con el reactivo de Jones.⁵³ En este caso sí se observó la oxidación del lactol mediante cromatografía en capa fina, pero al purificar el crudo de reacción se obtuvo la lactona **187** únicamente con un 20% de rendimiento (Esquema 4.24). Se pudo comprobar que este bajo rendimiento se debía a que bajo las condiciones ácidas de reacción el alcohol comienza a desprotegerse, eliminándose el grupo *tert*-butildifenilsililo. Los intentos por evitar esta desprotección realizando la reacción a baja temperatura no dieron buenos resultados ya que la desprotección comenzaba a observarse antes de que finalizara la reacción de oxidación. Por ello se decidió desproteger por completo la lactona con TBAF para aislar finalmente el compuesto **188** con un rendimiento del 55% para las dos etapas.

⁵³ a) K. Bowden, I. M. Heilbron, E. R. H. Jones, B. C. L. Weedon, *J. Chem. Soc.* **1946**, 39-45; b) E. R. H. Jones *et al.*, *J. Chem. Soc.* **1953**, 457, 2548, 3019; c) S. Valverde, A. Hernández, B. Herradón, R. M. Rabanal, M. Martín-Lomas, *Tetrahedron*, **1987**, 43, 3499-3504; b) S. Valverde, B. Herradón, R. M. Rabanal, M. Martín-Lomas, *Can. J. Chem.* **1987**, 65, 339-342.

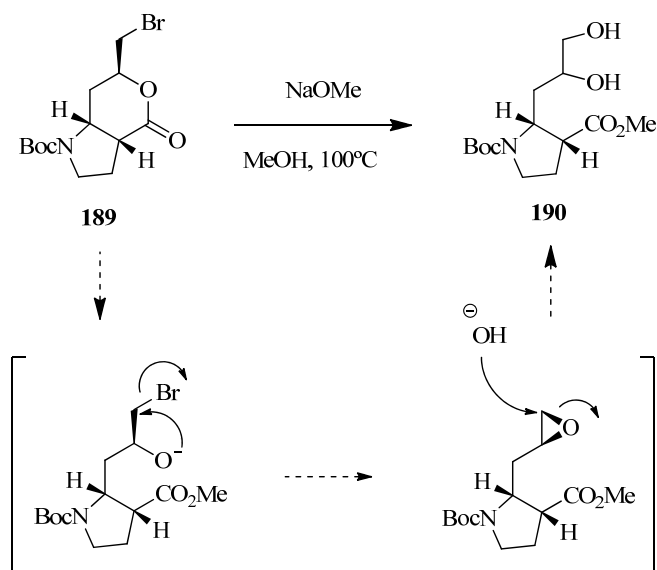
Esquema 4.24. Síntesis de la hidroxilactona **188**.

La reacción de dicha lactona **188** con tetrabromuro de carbono y trifenilfosfina permitió la instalación de un buen grupo saliente con el que llevar a cabo la posterior alquilación de la amina una vez desprotegida (Esquema 4.25).

Esquema 4.25. Síntesis del bromuro **189**.

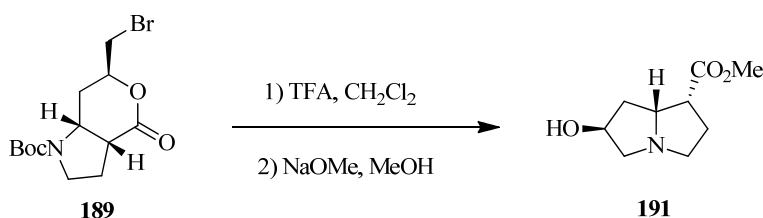
Antes de proceder a esta alquilación es necesaria la apertura de la lactona en presencia de metanol para obtener así el éster metílico de la posición C-1 de la amforoginina C. Al hacer reaccionar el compuesto **189** con carbonato potásico en metanol se recuperó la lactona inalterada. Se pensó entonces en emplear metóxido sódico en metanol y el resultado fue el diol **190** (Esquema 4.26). Dicho producto se forma a través de un epóxido intermedio fruto de la sustitución nucleófila del alcóxido resultante de la apertura de la lactona.⁵⁴ Posteriormente el epóxido se abre al correspondiente diol **190** durante el tratamiento de la reacción con una disolución acuosa.

⁵⁴ La formación de un epóxido en similares sustratos al llevar a cabo la apertura de una lactona con metóxido sódico en metanol ha sido anteriormente descrita: a) O. Varela, P. A. Zunsain, *J. Org. Chem.* **1993**, 58, 7860-7864; b) O. Varela, *Pure & Appl. Chem.* **1997**, 69, 621-626.



Esquema 4.26. Mecanismo de formación del diol **190**.

Basándonos en este mecanismo pensamos en la posibilidad de formar directamente el anillo de pirrolizidina por ataque nucleófilo de la amina sobre el epóxido intermedio.⁵⁵ La reacción del bromuro **189** con ácido trifluoroacético condujo a la amina libre que sin necesidad de ser purificada fue disuelta en metanol (Esquema 4.27). A continuación se añadió una disolución de metóxido sódico en metanol para poder obtener finalmente el compuesto **191**, que fue empleado en la siguiente reacción sin purificar dada su elevada polaridad.

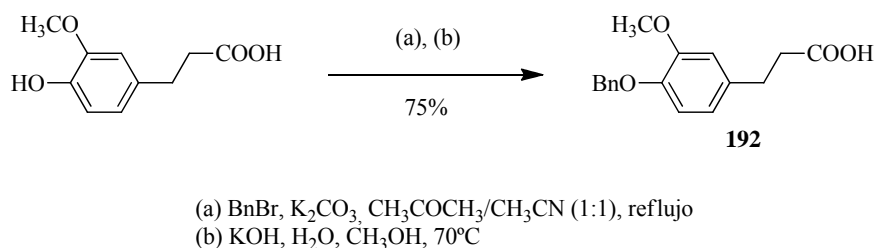


Esquema 4.27. Síntesis de la pirrolizidina **191**.

Una vez formado el anillo de pirrolizidina central de la amforoginina C con los sustituyentes adecuados en las posiciones C-1 y C-6, sólo se requiere formar el éster entre el hidroxilo libre y el ácido hidroferúlico. Para ello fue necesario proteger previamente el fenol libre de dicho ácido. Se escogió como grupo protector el grupo bencilo que permite una desprotección sencilla mediante hidrogenación y que ya fue empleado por el grupo de Yoda en la síntesis de la amforoginina A con buenos resultados. La protección se llevó a cabo con

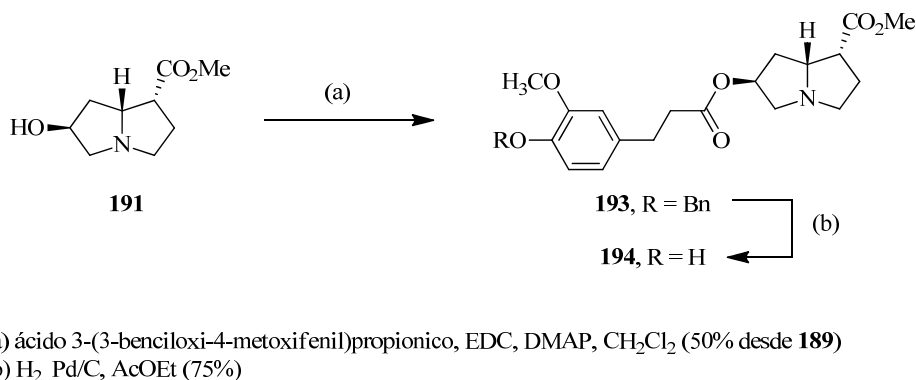
⁵⁵ V. Ratovelomanana, L. Vidal, J. Royer, H.-P. Husson, *Heterocycles*, **1991**, 32, 879-888.

bromuro de bencilo y carbonato potásico en una mezcla de acetona/acetonitrilo (1:1) a reflujo y posteriormente se trató con hidróxido potásico⁵⁶ para obtener el compuesto **192** con un 75% de rendimiento (Esquema 4.28).



Esquema 4.28. Protección del grupo fenólico del ácido hidroferúlico.

La posterior reacción de acoplamiento se realizó empleando 1-etil-3-(3-dimetilaminopropil) carbodiimida (EDC) y 4-dimetilaminopiridina (DMAP) en diclorometano para obtener el correspondiente éster **193** con un rendimiento del 50% desde el producto **189** (Esquema 4.29). La hidrogenación catalítica con Pd/C en AcOEt condujo finalmente a la amforoginina C (**194**) de la que se obtuvieron 21 mg y cuyos datos físicos y espectroscópicos coinciden con los descritos en la literatura.¹³



Esquema 4.29. Síntesis de la amforoginina C.

Finalmente se pudo confirmar la estructura y estereoquímica de la amforoginina C mediante un estudio de difracción de rayos X del producto cristalizado en metanol (Figura 4.10). Si bien el estudio de rayos X sólo pudo proporcionar la configuración relativa del compuesto, dada la ruta de síntesis partiendo del tri-*O*-acetil-*D*-glucal se puede confirmar la estereoquímica absoluta del producto obtenido.

⁵⁶ D. Li, B. Zhao, S.-P. Sim, T.-K. Li, A. Liu, L. F. Liu, E. J. LaVoie, *Bioorg. Med. Chem.* **2003**, *11*, 3795-3805.

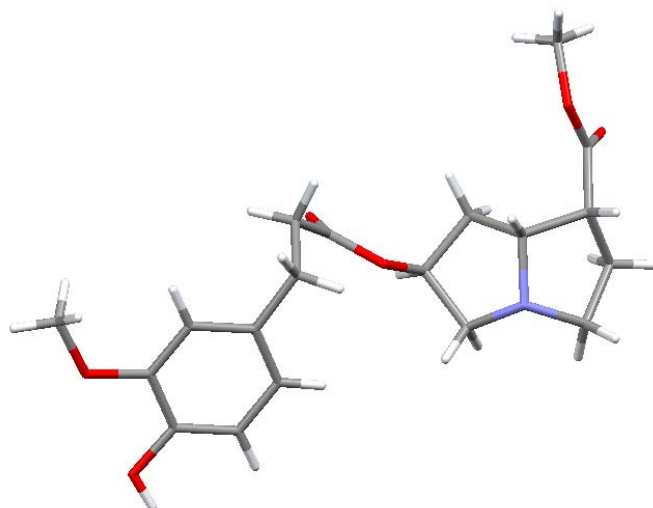


Figura 4.10. Estructura de difracción de rayos X de la amforoginina C.⁵⁷

De este modo hemos sido capaces de completar la primera síntesis total y estereoselectiva del alcaloide de pirrolizidina amforoginina C a través de una ruta de 20 etapas con un rendimiento global del 3% y empleando como pasos claves una transposición de Claisen-Johnson intramolecular y una cicloadición 1,3-dipolar azida-alqueno intramolecular.

⁵⁷ Los datos de difracción de rayos X de la amforoginina C se encuentran en el anexo II.

PARTE EXPERIMENTAL

4.4.- PARTE EXPERIMENTAL.

A continuación se presenta la parte experimental correspondiente al capítulo de la síntesis de la amforoginina C. Tanto los procedimientos como la caracterización de los productos están redactados en inglés. Todas las reacciones con reactivos sensibles se realizaron en atmósfera inerte (argón) y con disolventes secos. La mayoría de los reactivos utilizados se adquirieron en Aldrich o Fluka y se usaron sin purificar.

4.4.1.- Técnicas generales utilizadas.

Cromatografía

Las cromatografías en capa fina (CCF) se realizaron empleando placas de gel de sílice (Merck, 60 F_{4/254}) de 0,2 mm de espesor, visualizándose las manchas con luz UV (365 nm y 254 nm) o mediante reveladores químicos como ácido fosfomolibdico, permanganato potásico o ninhidrina.

Las cromatografías en columna se realizaron con gel de sílice (Merck, 230-240 mesh ASTM) utilizando la técnica de columna seca con elución a presión (Flash chromatography).¹ El eluyente empleado es indicado en cada caso.

Resonancia magnética nuclear²

Los espectros de resonancia magnética nuclear fueron realizados en los siguientes equipos: Varian-UNITY-500, Varian-INOVA-400, Varian-Mercury-400, Varian-INOVA-300 y Bruker-300. Los desplazamientos químicos se describen en partes por millón (δ) y las constantes de acoplamiento (J) se indican en hertzios (Hz). Los espectros de ¹H-RMN están referenciados respecto a la señal residual de protón del disolvente deuterado empleado en cada caso. La asignación de los distintos protones se hizo en base a experimentos bidimensionales tipo COSY, HSQC, HMBC y NOESY empleando la secuencia de pulsos estándar para cada uno de ellos. Cuando fue posible los protones diastereotópicos fueron designados con las letras α y β sin que deba considerarse como asignación estereoquímica de los mismos por analogía con la nomenclatura de esteroides. Los sistemas de spin complejos (2º orden; $\Delta\nu/J < 10$) fueron analizados como tales y las constantes de acoplamiento entre los distintos protones del sistema se calcularon cuando fue posible. Los espectros de ¹³C-RMN, desacoplados de protón en todos los casos, están referenciados respecto al desplazamiento químico de los correspondientes disolventes deuterados. La asignación de los distintos carbonos se hizo en algunos casos,

¹ W. C. Still; M. Khan; A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923-2925.

² T. D. W. Timothy en *High-resolution NMR techniques in organic chemistry*, Elsevier, **2009**.

basándose en experimentos bidimensionales tipo HSQC y HMBC. Si no se indica de otro modo, todos los espectros se registraron a temperatura ambiente.

Infrarrojo

Los espectros de infrarrojo (IR) se registraron en un espectrofotómetro modelo Perkin-Elmer-Spectrum One FT-IR. Las frecuencias del espectro se indican en cm^{-1} .

Espectros de masas

Los espectros de masa exacta (HRMS) de los compuestos fueron obtenidos con un espectrómetro de masas modelo Agilent 6520-Accurate-Mass LC/MS Q-TOF.

Puntos de fusión

Los puntos de fusión se midieron en una aparato de platina calentable tipo Kofler y están sin corregir.

Rotación óptica

Los poderes rotatorios ($[\alpha]_D$) se midieron en un polarímetro Perkin-Elmer 241 MC a temperatura ambiente, con las concentraciones y disolventes indicados en cada caso.

Rayos X

La difracción de rayos X se realizó en el Servicio Interdepartamental de Investigación (SIIdI) de la Universidad Autónoma de Madrid.

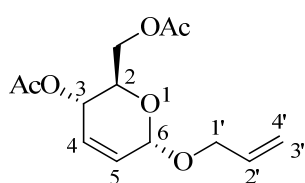
Microondas

Las reacciones llevadas a cabo en microondas se hicieron en un equipo CEM Discover equipado con agitación electromagnética y un sistema de control de la temperatura y la potencia.

4.4.2.- Synthesis of the hexahydropyrano[4,3-*b*]pyrrole core.

Ferrier rearrangement. Synthesis of (2*R*,3*S*,6*S*)-6-allyloxy-2-(acetoxymethyl)-3,6-dihydro-2*H*-pyran-3-yl acetate (**171**).

A 1M solution of FeCl₃ in CH₃CN (6.9 mL, 6.98 mmol) was added to a stirred solution of 3,4,6-tri-*O*-acetyl-*D*-glucal (19.0 g, 69.8 mmol) and allyl alcohol (5.2 mL, 76.8 mmol) in anhydrous CH₃CN (250 mL) under argon. The mixture was stirred for 30 minutes and saturated solution of NaHCO₃ was added. The aqueous phase was thoroughly extracted with CH₂Cl₂, and the combined organic phases were dried with MgSO₄. Solvent evaporation and purification of the residual product by flash chromatography gave diacetate **171** (17.1 g, 91%) as a white solid (mixture of anomers α/β ratio 8:1).



¹H-NMR (300 MHz, CDCl₃): δ 6.00 (dddd, 1H, $J_{2',4'} = 17.4$, $J_{2',3'} = 10.3$, $J_{2',1'\beta} = 6.3$, $J_{2',1'\alpha} = 5.2$ Hz, H-2'), 5.89 (m, 2H, H-5, H-4), 5.31 (m, 1H, H-3), 5.30 (ddd, 1H, $J_{4',2'} = 17.4$, $J_{4',3'} = 1.7$, $J_{4',1'\alpha} = 1.6$ Hz, H-4'), 5.20 (ddd, 1H, $J_{3',2'} = 10.3$, $J_{3',4'} = 1.7$, $J_{3',1'\beta} = 1.2$ Hz, H-3'), 5.07 (s, 1H, H-6), 4.30 (ddd, 1H, $J_{1'\alpha,1'\beta} = 12.6$, $J_{1'\alpha,2'} = 5.2$, $J_{1'\alpha,4'} = 1.6$ Hz, H-1' α), 4.21 (m, 2H, 2H-7), 4.09 (m, 1H, H-2), 4.07 (ddd, 1H, $J_{1'\beta,1'\alpha} = 12.6$, $J_{1'\beta,2'} = 6.3$, $J_{1'\beta,3'} = 1.2$ Hz, H-1' β), 2.10 (s, 3H, OCOCH₃), 2.08 (s, 3H, OCOCH₃).

¹³C-NMR (75 MHz, CDCl₃): δ 171.6 (OCOCH₃), 171.2 (OCOCH₃), 135.2 (C-2'), 130.3 (C-4), 128.8 (C-5), 118.4 (CH=CH₂), 94.7 (C-6), 70.3 (C-1'), 68.1 (C-2), 66.4 (C-3), 64.0 (C-7), 21.9 (OCOCH₃), 21.7 (OCOCH₃).

FTIR (KBr) ν_{\max} : 2902, 1744, 1371, 1235, 1043 cm⁻¹.

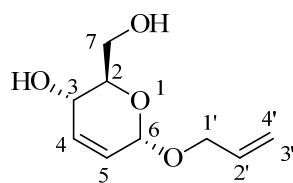
HRMS-ESI (*m/z*): calcd for C₁₃H₁₈NaO₆ [*M*+Na]⁺: 293.0996, found: 293.0993

[α]_D = + 109.0 (*c* = 1.0, CHCl₃)

Mp: 44-45°C

Synthesis of (2*R*,3*S*,6*S*)-6-allyloxy-2-(hydroxymethyl)-3,6-dihydro-2*H*-pyran-3-ol (**172**).

KOH (100 mg) was added to a solution of diacetate **171** (16.5 g, 61.0 mmol) in MeOH (150 mL). The mixture was stirred for 2 hours. The solvent was evaporated, and the residual product was purified by flash chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc). Diol **172** was obtained (11.3 g, 99%) as white solid (mixture of anomers α/β ratio 8:1).



¹H-NMR (300 MHz, CDCl₃): δ 5.94 (dd, 1H, $J_{4,5} = 10.1$, $J_{4,3} = 1.3$ Hz, H-4), 5.88 (dddd, 1H, $J_{2',4'} = 17.2$, $J_{2',3'} = 10.4$, $J_{2',1'\beta} = 6.3$, $J_{2',1'\alpha} = 5.3$ Hz, H-2'), 5.72 (dd, 1H, $J_{5,4} = 10.1$, $J_{5,6} = 2.2$ Hz, H-5), 5.27 (ddd, 1H, $J_{4',2'} = 17.2$, $J_{4',3'} = 1.6$, $J_{4',1'\alpha} = 1.6$ Hz, H-4'), 5.17 (ddd, 1H, $J_{3',2'} = 10.4$, $J_{3',4'} = 1.6$, $J_{3',1'\beta} = 1.2$ Hz, H-3'), 4.99 (s, 1H, H-6), 4.22 (ddd, 1H, $J_{1'\alpha,1'\beta} = 12.7$, $J_{1'\alpha,2'} = 5.3$, $J_{1'\alpha,4'} = 1.6$ Hz, H-1'α), 4.16 (m, 1H, H-3), 4.04 (ddd, 1H, $J_{1'\beta,1'\alpha} = 12.7$, $J_{1'\beta,2'} = 6.3$, $J_{1'\beta,3'} = 1.2$ Hz, H-1'β), 3.81 (m, 2H, 2H-7), 3.66 (dt, 1H, $J_{2,3} = 9.1$, $J_{2,7} = 4.0$ Hz, H-2), 3.41 (broad s, 1H, OH), 2.90 (broad s, 1H, OH).

¹³C-NMR (75 MHz, CDCl₃): δ 134.3 (C-2'), 133.7 (C-4), 126.0 (C-5), 117.5 (CH=CH₂), 93.6 (C-6), 71.6 (C-2), 69.2 (C-1'), 64.1 (C-3), 62.6 (C-7).

FTIR (KBr) ν_{\max} : 3391, 2879, 1396, 1043 cm⁻¹.

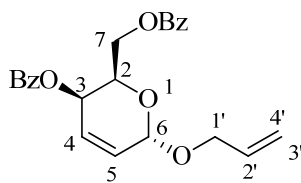
HRMS-ESI (m/z): calcd for C₉H₁₄NaO₄ [M+Na]⁺: 209.0784, found: 209.0779

[α]_D = + 72.0 (c = 1.2, CHCl₃)

Mp: 69-70°C

Mitsunobu reaction. Synthesis of (2R,3R,6S)-6-allyloxy-2-(benzoyloxymethyl)-3,6-dihydro-2H-pyran-3-yl benzoate (173).

DIAD (18.7 mL, 94.5 mmol) was added dropwise to a well stirred solution of diol **172** (8.0 g, 43.0 mmol), Ph₃P (24.7 g, 94.5 mmol), and benzoic acid (11.5 g, 94.5 mmol) in anhydrous THF (60 mL) under argon. Stirring was continued for 2 hours, after which the solvent was evaporated, and the residual product was purified by flash chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc). Compound **173** was obtained (16.0 g, 95%) as colorless thick oil (mixture of anomers α/β ratio 8:1).



¹H-NMR (300 MHz, CDCl₃): δ 8.05 (m, 4H, Ar-H), 7.56 (m, 2H, Ar-H), 7.43 (m, 4H, Ar-H), 6.30 (dd, 1H, $J_{4,5} = 10.0$, $J_{4,3} = 5.4$ Hz, H-4), 6.12 (dd, 1H, $J_{5,4} = 10.0$, $J_{5,6} = 3.1$ Hz, H-5), 5.94 (dddd, 1H, $J_{2',4'} = 17.2$, $J_{2',3'} = 10.3$, $J_{2',1'\beta} = 6.3$, $J_{2',1'\alpha} = 5.2$ Hz, H-2'), 5.37 (dd, 1H, $J_{3,4} = 5.4$, $J_{3,2} = 1.6$ Hz, H-3), 5.25 (dd, 1H, $J_{4',2'} = 17.2$, $J_{4',3'} = 1.6$ Hz, H-4'), 5.20 (d, 1H, $J_{6,5} = 3.1$ Hz, H-6), 5.17 (dd, 1H, $J_{3',2'} = 10.3$, $J_{3',4'} = 1.6$ Hz, H-3'), 4.67 (m, 2H, H-2, H-7α), 4.52 (m, 1H, H-7β), 4.29 (dd, 1H, $J_{1'\alpha,1'\beta} = 12.6$, $J_{1'\alpha,2'} = 5.2$ Hz, H-1'α), 4.05 (dd, 1H, $J_{1'\beta,1'\alpha} = 12.6$, $J_{1'\beta,2'} = 6.3$ Hz, H-1'β).

¹³C-NMR (75 MHz, CDCl₃): δ 166.4 (OCOPh), 166.1 (OCOPh), 134.3 (C-2'), 133.6 (Ar-C), 133.4 (Ar-C), 131.1 (C-5), 130.4 (Ar-C), 130.0 (3C, Ar-C), 129.9 (2C, Ar-C), 128.7 (2C, Ar-C),

128.6 (2C, Ar-C), 125.6 (C-4), 117.9 (CH=CH₂), 93.4 (C-6), 69.2 (C-1'), 67.6 (C-2), 63.8 (2C, C-3 and C-7).

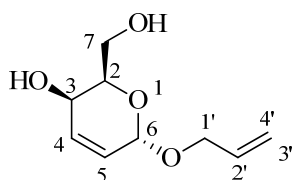
FTIR (neat) ν_{\max} : 2904, 1721, 1451, 1315, 1266, 1097, 1026 cm⁻¹.

HRMS-ESI (m/z): calcd for C₂₃H₂₂NaO₆ [M+Na]⁺: 417.1309, found: 417.1299

[α]_D = -189.0 (c = 1.0, CHCl₃)

Synthesis of (2R,3R,6S)-6-allyloxy-2-(hydroxymethyl)-3,6-dihydro-2H-pyran-3-ol (174).

A solution of dibenzoate **173** (6.0 g, 15.2 mmol) in MeOH (130 mL) was added to a solution of sodium methoxide (16.4 mg, 0.3 mmol) in MeOH (10 mL), and the mixture was stirred for 2 hours. The solvent was evaporated, and the residual product was purified by flash chromatography (silica gel, gradient from hexanes to 4:6 hexanes/EtOAc). Diol **174** was obtained (2.8 g, 99%) as a white solid (mixture of anomers α/β ratio 8:1).



¹H-NMR (300 MHz, CDCl₃): δ 6.12 (dd, 1H, $J_{4,5} = 10.0$, $J_{4,3} = 5.5$ Hz, H-4), 5.92 (dddd, 1H, $J_{2',4'} = 17.2$, $J_{2',3'} = 10.2$, $J_{2',1'\alpha} = 6.3$, $J_{2',1'\beta} = 5.3$ Hz, H-2'), 5.90 (dd, 1H, $J_{5,4} = 10.0$, $J_{5,6} = 3.1$ Hz, H-5), 5.27 (dd, 1H, $J_{4',2'} = 17.2$, $J_{4',3'} = 1.6$ Hz, H-4'), 5.18 (dd, 1H, $J_{3',2'} = 10.2$, $J_{3',4'} = 1.6$ Hz, H-3'), 5.07 (d, 1H, $J_{6,5} = 3.1$ Hz, H-6), 4.24 (dd, 1H, $J_{1'\alpha,1'\beta} = 12.7$, $J_{1'\alpha,2'} = 5.3$ Hz, H-1' α), 4.05 (dd, 1H, $J_{1'\beta,1'\alpha} = 12.7$, $J_{1'\beta,2'} = 6.3$ Hz, H-1' β), 4.04 (m, 1H, H-2), 3.89 (m, 3H, 2H-7, H-3), 2.76 (broad s, 1H, OH), 2.65 (broad s, 1H, OH).

¹³C-NMR (75 MHz, CDCl₃): δ 134.7 (C-2'), 131.4 (C-4), 129.8 (C-5), 117.9 (CH=CH₂), 94.0 (C-6), 70.7 (C-2), 69.3 (C-1'), 63.2 (C-3), 63.0 (C-7).

FTIR (KBr) ν_{\max} : 3430, 2905, 1189, 1094, 1064 cm⁻¹.

HRMS-ESI (m/z): calcd for C₉H₁₄NaO₄ [M+Na]⁺: 209.0784, found: 209.0779

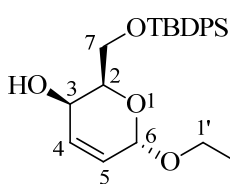
[α]_D = -101.0 (c = 1.0, CHCl₃)

Mp: 85-87°C

Protection of primary alcohol. Synthesis of (2R,3R,6S)-6-allyloxy-2-[(*tert*-butyldiphenylsilyloxy)methyl]-3,6-dihydro-2H-pyran-3-ol (175).

tert-Butyldiphenylsilyl chloride (10 mL, 38.6 mmol), Et₃N (5.86 mL, 42.1 mmol), and DMAP (635 mg, 5.2 mmol) were added to a solution of diol **174** (6.54 g, 35.1 mmol) in dry CH₂Cl₂ (100 mL) at 0°C under argon. The mixture was stirred overnight and allowed to warm

to room temperature. The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, gradient from hexanes to 6:4 hexanes/EtOAc) to afford compound **175** as a colorless oil (11.5 g, 77%).



¹H-NMR (400 MHz, CDCl₃): δ 7.70 (m, 4H, Ar-H), 7.40 (m, 6H, Ar-H), 6.18 (dd, 1H, $J_{4,5} = 9.9$, $J_{4,3} = 5.6$ Hz, H-4), 5.91 (m, 2H, H-2' and H-5), 5.26 (ddd, 1H, $J_{4',2'} = 17.2$, $J_{4',3'} = 1.7$, $J_{4',1'\alpha} = 1.6$ Hz, H-4'), 5.17 (ddd, 1H, $J_{3',2'} = 10.3$, $J_{3',4'} = 1.7$, $J_{3',1'\beta} = 1.3$ Hz, H-3'), 5.06 (d, 1H, $J_{6,5} = 2.9$ Hz, H-6), 4.24 (ddd, 1H, $J_{1'\alpha,1'\beta} = 12.7$, $J_{1'\alpha,2'} = 5.2$, $J_{1'\alpha,4'} = 1.6$, H-1'α), 4.13 (dt, 1H, $J = 6.2$, $J = 2.2$ Hz, H-2), 4.05 (ddd, 1H, $J_{1'\beta,1'\alpha} = 12.7$, $J_{1'\beta,2'} = 6.3$, $J_{1'\beta,3'} = 1.3$ Hz, H-1'β), 3.93 (m, 3H, 2H-7 and H-3), 1.90 (d, 1H, $J = 8.6$ Hz, OH), 1.07 (s, 9H, C(CH₃)₃).

¹³C-NMR (100 MHz, CDCl₃): δ 135.7 (d, 4C, Ar-C), 134.4 (C-2'), 133.4 (d, 2C, Ar-C), 129.9 (d, 3C, 2Ar-C and C-4), 128.7 (C-5), 127.9 (4C, Ar-C), 117.7 (CH=CH₂), 93.5 (C-6), 70.9 (C-2), 68.8 (C-1'), 63.6 (C-3), 62.0 (C-7), 26.9 (3C, C(CH₃)₃), 19.3 (C(CH₃)₃).

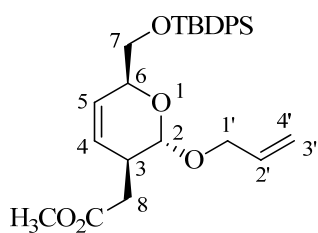
FTIR (neat) ν_{\max} : 3461, 3072, 3049, 2931, 2858, 1739, 1473, 1428, 1390, 1362, 1264, 1188, 1113, 1031, 823, 740, 703 cm⁻¹.

HRMS-ESI (m/z): calcd for C₂₅H₃₂NaO₄Si [M+Na]⁺: 447.1962, found: 447.1970

[α]_D = - 63.0 (c = 1.0, CHCl₃)

Claisen-Johnson rearrangement. Synthesis of methyl 2-[(2*S*,3*S*,6*S*)-2-allyloxy-6-[(*tert*-butyldiphenylsilanyloxy)-methyl]-3,6-dihydro-2*H*-pyran-3-yl]acetate (176**).**

A mixture of alcohol **175** (5.0 g, 11.8 mmol) and trimethyl orthoacetate (22 mL) was heated to 100°C, and then propionic acid (0.09 mL, 1.18 mmol) was added. The mixture was stirred for 72 hours at 140°C (MeOH formed during the reaction was eliminated periodically with a rotavapor). The solvent was evaporated, and the residual product was purified by flash chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc). Ester **176** was obtained (4.82 g, 85%) as a colorless thick oil.



¹H-NMR (400 MHz, CDCl₃): δ 7.68 (m, 4H, Ar-H), 7.41 (m, 6H, Ar-H), 5.93 (dddd, 1H, $J_{2',4'} = 17.2$, $J_{2',3'} = 10.4$, $J_{2',1'\beta} = 6.2$, $J_{2',1'\alpha} = 5.2$ Hz, H-2'), 5.79 (m, 2H, H-4 and H-5), 5.29 (ddd, 1H, $J_{4',2'} = 17.2$, $J_{4',3'} = 1.7$, $J_{4',1'\alpha} = 1.6$ Hz, H-4'), 5.18 (ddd, 1H, $J_{3',2'} = 10.4$, $J_{3',4'} = 1.7$, $J_{3',1'\beta} = 1.3$ Hz, H-3'), 4.80 (s, 1H, H-2), 4.26-4.20 (m, 2H, H-6 and H-1'α), 4.06 (ddd, 1H, $J_{1'\beta,1'\alpha} = 13.0$, $J_{1'\beta,2'} = 6.2$, $J_{1'\beta,3'} = 1.3$ Hz, H-1'β), 3.73 (m, 2H, 2H-7), 3.67 (s, 3H, CO₂CH₃), 2.60 (m, 1H, H-3), 2.48 (dd, 1H, $J_{8\alpha,8\beta} = 16.1$, $J_{8\alpha,3} = 8.1$ Hz, H-8α), 2.36 (dd, 1H, $J_{8\beta,8\alpha} = 16.1$, $J_{8\beta,3} = 6.6$ Hz, H-8β), 1.07 (s, 9H, C(CH₃)₃).

^{13}C -NMR (100 MHz, CDCl_3): δ 172.5 (C=O), 135.8 (d, 4C, Ar-C), 134.4 (d, C-2'), 133.6 (d, 2C, Ar-C), 129.8 (d, 2C, Ar-C), 127.8 (d, 4C, Ar-C), 127.0 (C-5), 126.0 (C-4), 117.4 (CH=CH₂), 98.2 (C-2), 69.5 (C-6), 68.6 (C-1'), 66.3 (C-7), 51.8 (CO₂CH₃), 37.8 (C-8), 35.8 (C-3), 27.0 (3C, C(CH₃)₃), 19.4 (C(CH₃)₃).

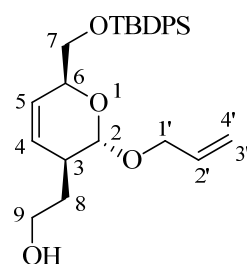
FTIR (neat) ν_{max} : 3072, 3048, 2931, 2858, 1739, 1647, 1590, 1473, 1428, 1391, 1361, 1267, 1113, 1027, 933, 823, 794, 740, 702 cm⁻¹.

HRMS-ESI (m/z): calcd for C₂₈H₄₀NO₅Si [M+NH₄]⁺: 498.2670, found: 498.2668

$[\alpha]_{\text{D}}$ = + 29.5 (c = 1.1, CHCl₃)

Reduction of methyl ester. Synthesis of 2-[(2*S*,3*S*,6*S*)-2-(allyloxy)-6-[(*tert*-butyldiphenylsilanyloxy)-methyl]-3,6-dihydro-2*H*-pyran-3-yl]ethanol (177**).**

Lithium borohydride (272 mg, 12.5 mmol) was added to a solution of compound **176** (2.0 g, 4.16 mmol) in anhydrous THF (10 mL) at 0°C. Then MeOH (1 mL) was added dropwise. The reaction was stirred for 30 minutes at 0°C and then at room temperature for another 4 hours. The reaction was cooled again to 0°C and quenched with addition of H₂O. The MeOH was evaporated and the residue was extracted with EtOAc (3 X 60 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated in vacuo. The crude was purified by chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) to provided compound **177** (1.69 g, 90%) as a colorless oil.



^1H -NMR (300 MHz, CDCl_3): δ 7.69 (m, 4H, Ar-H), 7.40 (m, 6H, Ar-H), 5.94 (dddd, 1H, $J_{2',4'} = 17.2$, $J_{2',3'} = 10.4$, $J_{2',1'\beta} = 6.2$, $J_{2',1'\alpha} = 5.2$ Hz, H-2'), 5.85 (m, 1H, H-4), 5.75 (m, 1H, H-5), 5.28 (ddd, 1H, $J_{4',2'} = 17.2$, $J_{4',3'} = 1.6$, $J_{4',1'\alpha} = 1.5$ Hz, H-4'), 5.19 (ddd, 1H, $J_{3',2'} = 10.4$, $J_{3',4'} = 1.6$, $J_{3',1'\beta} = 1.0$ Hz, H-3'), 4.88 (s, 1H, H-2), 4.23 (m, 2H, H-6 and H-1' α), 4.05 (ddd, 1H, $J_{1'\beta,1'\alpha} = 12.9$, $J_{1'\beta,2'} = 6.2$, $J_{1'\beta,3'} = 1.0$ Hz, H-1' β), 3.80-3.59 (m, 4H, 2H-7 and 2H-9), 2.33 (m, 1H, H-3), 2.19 (broad s, 1H, OH), 1.73 (m, 2H, 2H-8), 1.07 (s, 9H, C(CH₃)₃).

^{13}C -NMR (75 MHz, CDCl_3): δ 135.8 (d, 4C, Ar-C), 134.4 (C-2'), 133.6 (d, 2C, Ar-C), 129.8 (t, 2C, Ar-C), 127.8 (4C, Ar-C), 126.7 (d, C-5), 126.0 (C-4), 117.5 (CH=CH₂), 99.5 s, (C-2), 69.3 (C-6), 68.5 (C-1'), 66.3 (C-7), 59.9 (C-9), 36.9 (C-3), 35.9 (C-8), 27.0 (3C, C(CH₃)₃), 19.4 (d, C(CH₃)₃).

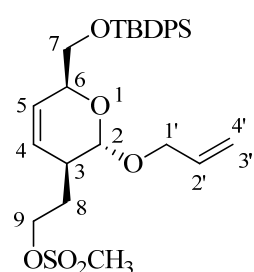
FTIR (neat) ν_{max} : 3072, 3048, 2931, 2859, 1473, 1428, 1187, 1113, 1031, 823, 740, 703 cm⁻¹.

HRMS-ESI (m/z): calcd for C₂₇H₃₆NaO₄Si [M+Na]⁺: 475.2275, found: 475.2262

$[\alpha]_D = +51.0$ ($c = 1.0$, CHCl_3)

Synthesis of 2-[(2*S*,3*S*,6*S*)-2-(allyloxy)-6-[(*tert*-butyldiphenylsilanyloxy)-methyl]-3,6-dihydro-2*H*-pyran-3-yl]ethyl methanesulfonate (178**).**

Et_3N (0.74 mL, 5.30 mmol) was added to a solution of **177** (1.0 g, 2.21 mmol) in CH_2Cl_2 (30 mL) at 0°C followed by dropwise addition of methanesulfonyl chloride (0.22 mL, 2.88 mmol) dissolved in 5 mL of CH_2Cl_2 . The reaction was stirred for 30 minutes at 0°C and then 2 hours at room temperature. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (silica gel, gradient from hexanes to 8:2 hexanes/EtOAc) to afford compound **178** (1.12 g, 96%) as a colorless oil.



$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.69 (m, 4H, Ar-H), 7.41 (m, 6H, Ar-H), 5.93 (dddd, 1H, $J_{2',4'} = 17.2$, $J_{2',3'} = 10.3$, $J_{2',1'\beta} = 6.3$, $J_{2',1'\alpha} = 5.2$ Hz, H-2'), 5.82 (m, 2H, H-4 and H-5), 5.29 (ddd, 1H, $J_{4',2'} = 17.2$, $J_{4',3'} = 1.7$, $J_{4',1'\alpha} = 1.6$ Hz, H-4'), 5.20 (ddd, 1H, $J_{3',2'} = 10.3$, $J_{3',4'} = 1.7$, $J_{3',1'\beta} = 1.3$ Hz, H-3'), 4.78 (s, 1H, H-2), 4.26 (m, 4H, H-6, H-1' α and 2H-9), 4.05 (ddd, 1H, $J_{1'\beta,1'\alpha} = 12.9$, $J_{1'\beta,2'} = 6.3$, $J = 1.6$ Hz, H-1' β), 3.75 (m, 2H, 2H-7), 2.97 (s, 3H, OSO_2CH_3), 2.31 (m, 1H, H-3), 1.96 (ddt, 1H, $J_{8\alpha,8\beta} = 13.7$, $J_{8\alpha,3} = 6.9$, $J_{8\alpha,9} = 6.9$ Hz, H-8 α), 1.83 (ddt, 1H, $J_{8\beta,8\alpha} = 13.9$, $J_{8\beta,3} = 7.6$, $J_{8\beta,9} = 6.2$ Hz, H-8 β), 1.07 (s, 9H, $\text{C}(\text{CH}_3)_3$).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 135.7 (d, 4C, Ar-C), 134.3 (d, C-2'), 133.6 (d, 2C, Ar-C), 129.8 (d, 2C, Ar-C), 127.8 (d, 4C, Ar-C), 127.4 (C-5), 125.6 (C-4), 117.6 ($\text{CH}=\text{CH}_2$), 98.6 (C-2), 69.6 (C-6), 68.5 (C-1'), 67.5 (C-9), 66.2 (C-7), 37.6 (OSO_2CH_3), 35.7 (C-3), 33.0 (C-8), 27.0 (3C, $\text{C}(\text{CH}_3)_3$), 19.4 ($\text{C}(\text{CH}_3)_3$).

FTIR (neat) ν_{max} : 3072, 3032, 2931, 2858, 1736, 1647, 1589, 1473, 1428, 1359, 1176, 1114, 1030, 958, 823, 796, 742, 704 cm^{-1} .

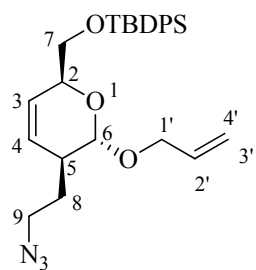
HRMS-ESI (m/z): calcd for $\text{C}_{28}\text{H}_{38}\text{NaO}_6\text{SSi}$ [$\text{M}+\text{Na}$] $^+$: 553.2051, found: 553.2046

$[\alpha]_D = +47.4$ ($c = 1.0$, CHCl_3)

Synthesis of [(2*S*,5*S*,6*S*)-6-(allyloxy)-5-(2-azidoethyl)-5,6-dihydro-2*H*-pyran-2-yl]methoxy}(*tert*-butyl)diphenylsilane (179**).**

Mesylate **178** (800 mg, 1.51 mmol) was dissolved in anhydrous DMF (10 mL). Sodium azide (980 mg, 15.1 mmol) was added and the mixture was heated to 60°C for 2 hours. Then the

solvent was removed in vacuo. The residue was dissolved in water and extracted with EtOAc (3 X 40 mL). The combined organic phases were dried over MgSO_4 , filtered and concentrated in vacuo. The crude was purified by column chromatography (silica gel, gradient from hexanes to 85:15 hexanes/EtOAc) to yield **179** (691 mg, 96%) as a colorless oil.



$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.68 (m, 4H, Ar-H), 7.40 (m, 6H, Ar-H), 5.92 (dddd, 1H, $J_{2',4'} = 17.2$, $J_{2',3'} = 10.3$, $J_{2',1'\beta} = 6.3$, $J_{2',1'\alpha} = 5.2$ Hz, H-2'), 5.79 (m, 2H, H-3 and H-4), 5.28 (ddd, 1H, $J_{4',2'} = 17.2$, $J_{4',3'} = 1.7$, $J_{4',1'\alpha} = 1.6$ Hz, H-4'), 5.19 (ddd, 1H, $J_{3',2'} = 10.3$, $J_{3',4'} = 1.7$, $J_{3',1'\beta} = 1.3$ Hz, H-3'), 4.75 (s, 1H, H-6), 4.22 (m, 2H, H-2 and H-1' α), 4.05 (ddd, 1H, $J_{1'\beta,1'\alpha} = 12.8$, $J_{1'\beta,2'} = 6.3$, $J_{1'\beta,3'} = 1.3$ Hz, H-1' β), 3.73 (m, 2H, 2H-7), 3.32 (m, 2H, 2H-9), 2.23 (m, 1H, H-5), 1.71 (m, 2H, 2H-8), 1.07 (s, 9H, $\text{C}(\text{CH}_3)_3$).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 135.8 (d, 4C, Ar-C), 134.4 (C-2'), 133.7 (d, 2C, Ar-C), 129.8 (d, 2C, Ar-C), 127.8 (d, 4C, Ar-C), 127.0 (C-3), 125.9 (C-4), 117.5 ($\text{CH}=\text{CH}_2$), 98.8 (C-6), 69.5 (C-2), 68.5 (C-1'), 66.4 (C-7), 49.0 (C-9), 36.7 (C-5), 32.6 (C-8), 27.0 (3C, $\text{C}(\text{CH}_3)_3$), 19.4 ($\text{C}(\text{CH}_3)_3$).

FTIR (neat) ν_{max} : 3072, 3048, 2931, 2859, 2096, 1473, 1463, 1428, 1362, 1261, 1187, 1114, 1033, 823, 702 cm^{-1} .

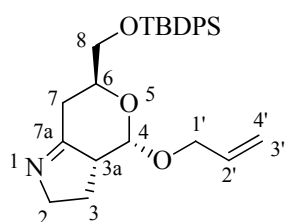
HRMS-ESI (m/z): calcd for $\text{C}_{27}\text{H}_{35}\text{N}_3\text{NaO}_3\text{Si}$ $[\text{M}+\text{Na}]^+$: 500.2340, found: 500.2316

$[\alpha]_{\text{D}} = +67.2$ ($c = 1.0$, CHCl_3)

1,3-Dipolar cycloaddition of compound **179**.

A solution of compound **179** (300 mg, 0.63 mmol) in toluene (6 mL) was heated in a sealed tube at 140°C for 24 hours. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, gradient from CH_2Cl_2 to 97:3 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford the desired imina **180** (192 mg, 68%) as a pale yellow viscous oil and the aziridine **181** (45 mg, 16%) as a dark yellow oil.

(3a*R*,4*S*,6*S*)-4-(allyloxy)-6-[(*tert*-butyldiphenylsilanyloxy)-methyl]-2,3,3a,4,6,7-hexahydropyrano[4,3-*b*]pyrrole (**180**).



$^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 7.69 (m, 4H, Ar-H), 7.39 (m, 6H, Ar-H), 5.86 (dddd, 1H, $J_{2',4'} = 17.2$, $J_{2',3'} = 10.7$, $J_{2',1'\beta} = 5.9$, $J_{2',1'\alpha} = 4.9$ Hz, H-2'), 5.23 (ddd, 1H, $J_{4',2'} = 17.2$, $J_{4',3'} = 1.7$, $J_{4',1'\alpha} = 1.6$ Hz, H-4'), 5.14 (ddd, 1H, $J_{3',2'} = 10.7$, $J_{3',4'} = 1.7$, $J_{3',1'\beta} = 1.3$ Hz, H-3'),

5.09 (d, 1H, $J_{4,3a} = 4.7$ Hz, H-4), 4.16 (ddd, 1H, $J_{1'\alpha,1'\beta} = 13.3$, $J_{1'\alpha,2'} = 4.9$, $J_{1'\alpha,4'} = 1.6$ Hz, H-1' α), 3.94 (m, 3H, H-1' β , H-6 and H-8 α), 3.79 (dd, 1H, $J_{2\alpha,2\beta} = 10.7$, $J = 5.6$ Hz, H-2 α), 3.72 (m, 2H, H-2 β and H-8 β), 2.93 (m, 1H, H-3a), 2.65 (dd, 1H, $J_{7\alpha,7\beta} = 14.0$, $J_{7\alpha,6} = 2.9$ Hz, H-7 α), 2.30 (m, 1H, H-7 β), 1.90 (m, 2H, 2H-3), 1.06 (s, 9H, C(CH₃)₃).

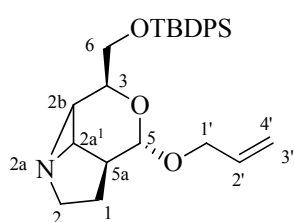
¹³C-NMR (125 MHz, CDCl₃): δ 172.8 (C=N), 135.7 (d, 4C, Ar-C), 134.1 (C-2'), 133.5 (d, 2C, Ar-C), 129.8 (d, 2C, Ar-C), 127.8 (4C, Ar-C), 116.9 (CH=CH₂), 98.5 (C-4), 69.2 (C-6), 67.7 (C-1'), 66.7 (C-2), 60.2 (C-8), 51.6 (C-3a), 34.4 (C-7), 26.9 (3C, C(CH₃)₃), 22.8 (C-3), 19.4 (C(CH₃)₃).

FTIR (neat) ν_{\max} : 3071, 3049, 2956, 2930, 2859, 1663, 1473, 1463, 1428, 1362, 1287, 1136, 1113, 1031, 824, 703 cm⁻¹.

HRMS-ESI (m/z): calcd for C₂₇H₃₆NO₃Si [M+H]⁺: 450.2459, found: 450.2474

$[\alpha]_D = +110.5$ (c = 0.88, CHCl₃)

(3*S*,5*S*,5*aS*)-5-(allyloxy)-3-[(*tert*-butyldiphenylsilanyloxy)-methyl]hexahydro-1*H*-4-oxa-2*a*-azacyclopropa[*cd*]indene (181).



¹H-NMR (300 MHz, CDCl₃): δ 7.72 (m, 4H, Ar-H), 7.40 (m, 6H, Ar-H), 5.93 (dddd, 1H, $J_{2',4'} = 17.2$, $J_{2',3'} = 10.3$, $J_{2',1'\beta} = 6.2$, $J_{2',1'\alpha} = 5.2$ Hz, H-2'), 5.29 (dd, 1H, $J_{4',2'} = 17.2$, $J_{4',3'} = 1.6$ Hz, H-4'), 5.20 (dd, 1H, $J_{3',2'} = 10.3$, $J_{3',4'} = 1.6$ Hz, H-3'), 4.60 (s, 1H, H-5), 4.34 (td, 1H, $J = 6.2$, $J = 2.3$ Hz, H-3), 4.15 (ddt, 1H, $J_{1'\alpha,1'\beta} = 12.9$, $J_{1'\alpha,2'} = 5.2$, $J = 1.5$ Hz, H-1' α), 4.01-3.87 (m, 3H, H-1' β and 2H-6), 3.05 (m, 1H, H-2 α), 2.81 (m, 2H, H-2 β and H-2a¹), 2.41 (m, 2H, H-5a and H-1 α), 2.16 (m, 1H, H-2b), 1.81 (m, 1H, H-1 β), 1.08 (s, 9H, C(CH₃)₃).

¹³C-NMR (75 MHz, CDCl₃): δ 135.8 (d, 4C, Ar-C), 134.3 (C-2'), 133.5 (2C, Ar-C), 129.8 (2C, Ar-C), 127.8 (4C, Ar-C), 117.6 (CH=CH₂), 98.0 (C-5), 67.9 (2C, C-3 and C-1'), 64.9 (C-6), 49.0 (C-2), 40.2 (C-2a¹), 38.4 (C-1), 37.1 (C-5a), 36.6 (C-2b), 26.9 (3C, C(CH₃)₃), 19.3 (C(CH₃)₃).

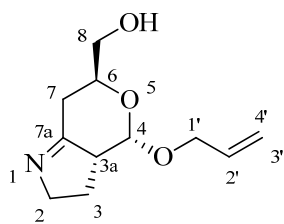
FTIR (neat) ν_{\max} : 3071, 3049, 2956, 2931, 2858, 1472, 1463, 1428, 1391, 1362, 1190, 1113, 1089, 1029, 999, 823, 740, 703 cm⁻¹.

HRMS-ESI (m/z): calcd for C₂₇H₃₆NO₃Si [M+H]⁺: 450.2459, found: 450.2478

$[\alpha]_D = +29.9$ (c = 0.97, CHCl₃)

Deprotection of the alcohol. Synthesis of [(3a*R*,4*S*,6*S*)-4-(allyloxy)-2,3,3a,4,6,7-hexahydropyrano[4,3-*b*]pyrrol-6-yl]methanol (182**).**

Tetrabutylammonium fluoride trihydrate (320 mg, 1.02 mmol) was added to a solution of **180** (230 mg, 0.51 mmol) in THF (10 mL). The mixture was stirred for 2 hours at room temperature. The solvent was evaporated and the residual oil was purified by flash chromatography (silica gel, gradient from CH₂Cl₂ to 96:4 CH₂Cl₂/MeOH) to afford **182** (87 mg, 81%) as a yellow oil.



¹H-NMR (300 MHz, CDCl₃): δ 5.84 (dddd, 1H, $J_{2',4'} = 17.2$, $J_{2',3'} = 10.4$, $J_{2',1'\beta} = 5.9$, $J_{2',1'\alpha} = 5.1$ Hz, H-2'), 5.22 (ddd, 1H, $J_{4',2'} = 17.2$, $J_{4',3'} = 1.7$, $J_{4',1'\alpha} = 1.6$ Hz, H-4'), 5.13 (ddd, 1H, $J_{3',2'} = 10.4$, $J_{3',4'} = 1.7$, $J_{3',1'\alpha} = 1.5$ Hz, H-3'), 5.08 (d, 1H, $J_{4,3a} = 4.6$ Hz, H-4), 4.14 (ddt, 1H, $J_{1'\alpha,1'\beta} = 13.3$, $J_{1'\alpha,2'} = 5.1$, $J_{1'\alpha,3'} = 1.5$ Hz, H-1'α), 3.97-3.84 (m, 3H, H-6, H-1'β and H-2α), 3.75-3.58 (m, 3H, 2H-8 and H-2β), 2.91 (m, 1H, H-3a), 2.57 (dd, 1H, $J_{7\alpha,7\beta} = 13.9$, $J_{7\alpha,6} = 3.1$ Hz, H-7α), 2.38 (m, 1H, H-7β), 1.88 (m, 2H, 2H-3).

¹³C-NMR (75 MHz, CDCl₃): δ 172.9 (C=N), 133.9 (C-2'), 117.1 (CH=CH₂), 98.8 (C-4), 69.1 (C-6), 67.9 (C-1'), 65.1 (C-8), 60.1 (C-2), 51.6 (C-3a), 33.5 (C-7), 22.8 (C-3).

FTIR (neat) ν_{\max} : 3233, 2914, 2871, 1664, 1461, 1424, 1370, 1344, 1314, 1288, 1132, 1032, 979, 955, 820, 731 cm⁻¹.

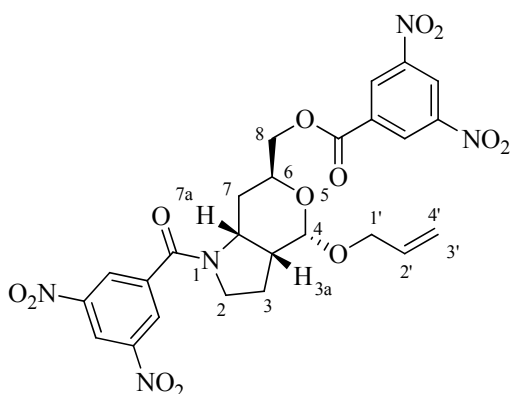
HRMS-ESI (m/z): calcd for C₁₁H₁₈NO₃ [M+H]⁺: 212.1281, found: 212.1291

[α]_D = +229.3 (c = 1.60, CHCl₃)

Synthesis of [(3a*R*,4*S*,6*S*,7a*R*)-4-(allyloxy)-1-(3,5-dinitrobenzoyl)octahydropyrano[4,3-*b*]pyrrol-6-yl]methyl 3,5-dinitrobenzoate (183**).**

Sodium borohydride (31 mg, 0.81 mmol) was added to a solution of compound **182** (86 mg, 0.41 mmol) in absolute ethanol (5 mL) at 0°C. After 45 minutes the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 X 30 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated in vacuo. The crude material was dissolved in CH₂Cl₂ (10 mL) and cooled to 0°C. Et₃N (0.23 mL, 1.63 mmol) and 3,5-dinitrobenzoyl chloride (281 mg, 1.22 mmol) were sequentially added. After stirring at room temperature for 8 hours the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄, filtered and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from hexanes to 6:4

hexanes/EtOAc) to afford compound **183** (48 mg, 19%) as a yellow solid. The relative stereochemistry of **183** was confirmed by X-ray crystallographic.³



¹H-NMR (400 MHz, CDCl₃): δ 9.25 (t, 1H, J = 2.1 Hz, Ar-H), 9.19 (d, 2H, J = 2.1 Hz, Ar-H), 9.12 (t, 1H, J = 2.1 Hz, Ar-H), 8.76 (d, 2H, J = 2.1 Hz, Ar-H), 6.01 (dddd, 1H, $J_{2',4'} = 17.1$, $J_{2',3'} = 10.6$, $J_{2',1'\beta} = 5.6$, $J_{2',1'\alpha} = 4.9$ Hz, H-2'), 5.36 (ddd, 1H, $J_{4',2'} = 17.1$, $J_{4',3'} = 1.7$, $J_{4',1'\alpha} = 1.6$ Hz, H-4'), 5.32 (dd, 1H, $J_{3',2'} = 10.6$, $J_{3',4'} = 1.5$, H-3'), 5.04 (d, 1H, $J_{4,3a} = 5.4$ Hz, H-4), 4.50 (d, 2H, J = 5.6 Hz, 2H-8), 4.38 (m, 3H, H-7a, H-6 and H-1' α), 4.07

(m, 2H, H-1' β and H-2 α), 3.32 (t, 1H, J = 9.0 Hz, H-2 β), 2.73 (m, 2H, H-3a and H-7 α), 2.04 (m, 1H, H-3 α), 1.96 (m, 2H, H-7 β and H-3 β).

¹³C-NMR (100 MHz, CDCl₃): δ 166.9 (C=O, amide), 162.4 (C=O, ester), 148.8 (2C, Ar-C), 148.6 (2C, Ar-C), 140.3 (2C, Ar-C), 133.7 (C-2'), 129.6 (2C, Ar-C), 128.1 (2C, Ar-C), 122.7 (Ar-C), 120.4 (Ar-C), 117.7 (CH=CH₂), 97.4 (C-4), 68.7 (C-8), 68.6 (C-1'), 62.1 (C-6), 54.8 (C-7a), 52.3 (C-2), 39.3 (C-3a), 27.0 (C-7), 26.5 (C-3).

FTIR (KBr) ν_{\max} : 3100, 2922, 1733, 1631, 1543, 1463, 1404, 1345, 1281, 1171, 1079, 1024, 921, 730, 721 cm⁻¹.

HRMS-ESI (m/z): calcd for C₂₅H₂₄N₅O₁₃ [M+H]⁺: 602.1365, found: 602.1365

[α]_D = + 0.09 (c = 1.40, CHCl₃)

Mp: 193-195°C

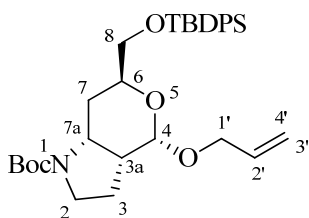
4.4.3.- Synthesis of amphorogynine C from the hexahydropyrano[4,3-*b*]pyrrole.

Synthesis of (3a*R*,4*S*,6*S*,7a*R*)-tert-butyl 4-(allyloxy)-6-[(tert-butyldiphenylsilyloxy)-methyl]hexahydropyrano[4,3-*b*]pyrrole-1(6*H*)-carboxylate (184).

To a solution of **180** (500 mg, 1.11 mmol) in MeOH (25 mL) at 0°C NaBH₄ (84 mg, 2.22 mmol) was added. After 30 minutes the reaction was warmed to room temperature and stirred for an additional hour. Then 10 mL of saturated NH₄Cl was added and the MeOH was eliminated under reduce pressure. The residue was diluted with aqueous NaOH solution (1 N, 10 mL) and thoroughly extracted with CH₂Cl₂ (3 X 40 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated in vacuo. The crude amine was dissolved in

³ Los datos de difracción de rayos X del compuesto **183** se encuentran en el anexo II.

CH₂Cl₂ (25 mL), cooled to 0°C. Et₃N (0.23 mL, 1.66 mmol) and (Boc)₂O (291 mg, 1.33 mmol) dissolved in CH₂Cl₂ (3 mL) were sequentially added. The reaction was left 30 minutes at 0°C and then 12 hours at room temperature. The solvent was eliminated under reduced pressure and the crude oil was purified by column chromatography (silica gel, gradient from hexanes to 9:1 hexanes/EtOAc) to obtain **184** (521 mg, 85%) as a colorless oil.



¹H-NMR (400 MHz, CDCl₃): δ 7.69 (m, 4H, Ar-H), 7.38 (m, 6H, Ar-H), 5.89 (dddd, 1H, $J_{2',4'} = 17.2$, $J_{2',3'} = 10.5$, $J_{2',1'\beta} = 5.3$, $J_{2',1'\alpha} = 4.9$ Hz, H-2'), 5.25 (d, 1H, $J_{4',2'} = 17.2$ Hz, H-4'), 5.14 (ddd, 1H, $J_{3',2'} = 10.5$, $J_{3',4'} = 1.6$, $J_{3',1'\alpha} = 1.4$ Hz, H-3'), 4.95 (d, 1H, $J_{4,3a} = 4.9$ Hz, H-4), 4.27 (m, 1H, H-1'α), 4.01-3.91 (m, 3H, H-1'β, H-6 and H-7a), 3.66 (m, 2H, 2H-8), 3.52 (m, 1H, H-2α), 3.42 (m, 1H, H-2β), 2.48 (m, 1H, H-3a), 2.30 (m, 1H, H-7α), 2.12 (m, 1H, H-7β), 1.95 (m, 1H, H-3α), 1.79 (m, 1H, H-3β), 1.46 (s, 9H, C(CH₃)₃ Boc), 1.05 (s, 9H, C(CH₃)₃ TBDPS).

¹³C-NMR (100 MHz, CDCl₃): δ 155.1 (C=O), 135.8 (4C, Ar-C), 134.8 (d, C-2'), 133.7 (d, 2C, Ar-C), 129.8 (2C, Ar-C), 127.8 (4C, Ar-C), 116.4 (d, CH=CH₂), 97.0 (C-4), 68.5 (C-1'), 67.6 (d, C-6), 66.8 s, (C-8), 53.4 (d, C-7a), 47.5 (d, C-2), 41.0 (C-3a), 28.0 (4C, C-7 and C(CH₃)₃ Boc), 27.4 (C(CH₃)₃ Boc) 27.1 (3C, C(CH₃)₃ TBDPS), 24.5 (C-3), 19.4 (C(CH₃)₃ TBDPS).

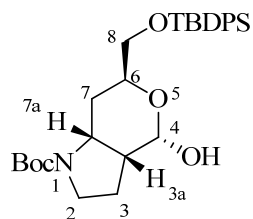
FTIR (neat) ν_{max}: 3072, 3050, 2931, 2859, 1811, 1757, 1694, 1474, 1456, 1428, 1393, 1366, 1262, 1211, 1172, 1113, 1034, 823, 740, 703, 614 cm⁻¹.

HRMS-ESI (m/z): calcd for C₃₂H₄₅NNaO₅Si [M+Na]⁺: 574.2959, found: 574.2975

[α]_D = - 3.89 (c = 0.93 CHCl₃)

Deallylation reaction.

184 (500 mg, 0.91 mmol) was dissolved in THF/H₂O (30 mL, 9:1) at room temperature. Then PdCl₂ (160 mg, 0.91 mmol) was added. After 8 hours 0.2 equivalents more of catalyst (32 mg, 0.18 mmol) were added and 0.2 equivalents more (32 mg, 0.18 mmol) after 24 hours. After 36 hours the reaction mixture was filtered through a plug of Celite. The filtrate was diluted with water and extracted with Et₂O (3 X 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography (silica gel, gradient from hexanes to 3:7 hexanes/EtOAc) to afford the lactol **186** as a mixture of diastereomers (354 mg, 85:15, 76%).

(3a*R*,4*S*,6*S*,7a*R*)-*tert*-butyl6-[(*tert*-butyldiphenylsilanyloxy)-methyl]-4-hydroxyhexahydropyrano[4,3-*b*]pyrrole-1(6*H*)-carboxylate.

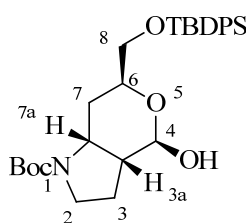
¹H-NMR (400 MHz, CDCl₃): δ 7.67 (m, 4H, Ar-H), 7.39 (m, 6H, Ar-H), 4.94 (d, 1H, $J_{4,3a} = 5.0$ Hz, H-4), 4.22 (m, 1H, H-8 α), 4.08 (d, 1H, $J_{8\beta,8\alpha} = 17.4$ Hz, H-8 β), 3.97 (m, 1H, H-7a), 3.91 (m, 1H, H-6), 3.54 (m, 2H, 2H-2), 2.51 (m, 1H, H-3a), 2.33 (m, 1H, H-7 α), 2.09 (m, 1H, H-7 β), 2.06 (m, 1H, H-3 α), 1.84 (m, 1H, H-3 β), 1.45 (s, 9H, C(CH₃)₃ Boc), 1.05 (s, 9H, C(CH₃)₃ TBDPS).

¹³C-NMR (100 MHz, CDCl₃): δ 155.1 (C=O), 135.8 (4C, Ar-C), 133.7 (2C, Ar-C), 129.9 (2C, Ar-C), 127.9 (4C, Ar-C), 98.0 (C-4), 72.7 (C-8), 68.1 (C-6), 53.2 (C-7a), 47.4 (C-2), 40.9 (C-3a), 28.8 (3C, C(CH₃)₃ Boc), 27.1 (4C, C-7 and C(CH₃)₃ TBDPS), 26.7 (C(CH₃)₃ Boc), 24.9 (C-3), 19.4 (C(CH₃)₃ TBDPS).

FTIR (neat) ν_{\max} : 3072, 3050, 2962, 2931, 2859, 1733, 1694, 1474, 1428, 1393, 1366, 1255, 1172, 1148, 1113, 1064, 824, 741, 704 cm⁻¹.

HRMS-ESI (m/z): calcd for C₂₉H₄₀NO₅Si [M-H]⁻: 510.2682, found: 510.2669

[α]_D = - 2.1 (c = 0.62, CHCl₃)

(3a*R*,4*R*,6*S*,7a*R*)-*tert*-butyl6-[(*tert*-butyldiphenylsilanyloxy)-methyl]-4-hydroxyhexahydropyrano[4,3-*b*]pyrrole-1(6*H*)-carboxylate.

¹H-NMR (400 MHz, CDCl₃): δ 7.67 (m, 4H, Ar-H), 7.39 (m, 6H, Ar-H), 4.69 (broad s, 1H, H-4), 4.06 (m, 1H, H-8 α), 3.99 (m, 1H, H-7a), 3.72-3.61 (m, 2H, H-8 β and H-6), 3.59 (m, 1H, H-2 α), 3.33 (ddd, 1H, $J_{2\beta,2\alpha} = 10.6$, $J = 8.6$, $J = 8.4$ Hz, H-2 β), 2.17 (m, 1H, H-3a), 1.84 (m, 2H, 2H-3), 1.75 (m, 2H, 2H-7), 1.46 (s, 9H, C(CH₃)₃ Boc), 1.06 (s, 9H, C(CH₃)₃ TBDPS).

¹³C-NMR (100 MHz, CDCl₃): δ 155.4 (C=O), 135.9 (4C, Ar-C), 133.5 (2C, Ar-C), 129.9 (2C, Ar-C), 127.9 (4C, Ar-C), 95.4 (C-4), 71.3 (C-6), 67.0 (C-8), 54.6 (C-7a), 46.5 (C-2), 43.9 (C-3a), 28.8 (C-7), 28.7 (3C, C(CH₃)₃ Boc), 27.1 (3C, C(CH₃)₃ TBDPS), 26.5 (2C, C(CH₃)₃ Boc and C-3), 19.5 (C(CH₃)₃ TBDPS).

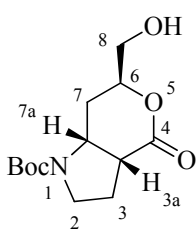
FTIR (neat) ν_{\max} : 3388, 2932, 2858, 1694, 1474, 1455, 1428, 1393, 1366, 1258, 1164, 1113, 1053, 824, 741, 703 cm⁻¹.

HRMS-ESI (m/z): calcd for C₂₉H₄₀NO₅Si [M-H]⁻: 510.2682, found: 510.2669

[α]_D = - 62.0 (c = 0.95 CHCl₃)

Synthesis of (3a*R*,6*S*,7a*R*)-*tert*-butyl 6-(hydroxymethyl)-4-oxohexahydropyrano[4,3-*b*]pyrrole-1(6*H*)-carboxylate (188).

Lactols **186** (180 mg, 0.35 mmol) were dissolved in acetone (10 mL) and some anhydrous magnesium sulfate was added. Then the solution was cooled to 0°C and a freshly prepared Jones reagent (2 mL) was added dropwise. After 30 minutes the reaction was allowed to warm to room temperature over one hour. Isopropyl alcohol (5 mL) was then added to destroy excess Jones reagent and the mixture was filtered through a small pad of Celite. The solvent was removed in vacuo and the crude was dissolved in NaHCO₃ solution and extracted with EtOAc (3 X 40 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated in vacuo. The crude oil was used in the next step without further purification. Tetrabutylammonium fluoride trihydrate (110 mg, 0.35 mmol) was added to a solution of crude lactone in THF (15 mL). The mixture was stirred for 2 hours at room temperature. The solvent was evaporated and the residual product was purified by flash chromatography (silica gel, gradient from hexanes to 2:8 hexanes/EtOAc) to afford **188** (52 mg, 55%, 2 steps) as a colorless oil.



¹H-NMR (500 MHz, CDCl₃): δ 4.47 (m, 1H, H-6), 4.21 (broad s, 1H, H-7a), 3.82 (d, 1H, *J*_{8α,8β} = 11.3 Hz, H-8α), 3.68 (dd, 1H, *J*_{8β,8α} = 11.3, *J*_{8β,6} = 4.9 Hz, H-8β), 3.52 (broad s, 1H, H-2α), 3.37 (dt, 1H, *J*_{2β,2α} = 11.1, *J* = 7.1 Hz, H-2β), 3.21 (m, 1H, H-3a), 2.33 (m, 1H, H-7α), 2.27 (m, 1H, H-3α), 2.19 (m, 1H, H-3β), 1.97 (ddd, 1H, *J*_{7β,7α} = 14.7, *J* = 10.5, *J* = 4.2 Hz, H-7β), 1.45 (s, 9H, C(CH₃)₃ Boc).

¹³C-NMR (125 MHz, CDCl₃): δ 172.4 (C-4), 154.4 (C=O, Boc), 77.0 (C-6), 64.5 (C-8), 53.5 (C-7a), 46.2 (C-2), 43.0 (C-3a), 29.4 (C-3), 28.4 (4C, C(CH₃)₃ Boc, C-7), 28.0 (C(CH₃)₃ Boc).

FTIR (neat) ν_{max}: 3444, 2976, 2935, 2880, 1732, 1694, 1399, 1367, 1260, 1167, 1096, 1049, 856, 773 cm⁻¹.

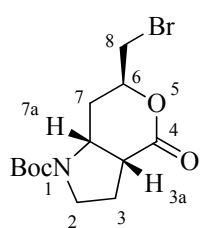
HRMS-ESI (m/z): calcd for C₁₃H₂₂NO₅ [M+H]⁺: 272.1492, found: 272.1495

[α]_D = - 89.3 (c = 2.5, CHCl₃)

Synthesis of (3a*R*,6*S*,7a*R*)-*tert*-butyl 6-(bromomethyl)-4-oxohexahydropyrano[4,3-*b*]pyrrole-1(6*H*)-carboxylate (189).

Lactone **188** (100 mg, 0.37 mmol) was dissolved in CH₂Cl₂ (10 mL) and cooled to 0°C. Carbon tetrabromide (185 g, 0.56 mmol) and triphenylphosphine (147 mg, 0.56 mmol) were added and the reaction was stirred at 0°C for 1 hour and then 2 hours at room temperature. Upon completion the solvent was removed in vacuo and the crude was purified by column

chromatography (silica gel, gradient from hexanes to 7:3 hexanes/EtOAc) to obtain **189** (87 mg, 70%) as a white solid.



$^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 4.55 (m, 1H, H-6), 4.19 (broad s, 1H, H-7a), 3.52 (m, 3H, 2H-8 and H-2 α), 3.36 (dt, 1H, $J_{2\beta,2\alpha} = 11.2$, $J_{2\beta,3\alpha} = J_{2\beta,3\beta} = 7.3$ Hz, H-2 β), 3.23 (m, 1H, H-3a), 2.59 (m, 1H, H-7a), 2.24 (m, 2H, 2H-3), 1.93 (ddd, 1H, $J_{7\beta,7\alpha} = 14.7$, $J = 10.6$, $J = 4.0$ Hz, H-7 β), 1.47 (s, 9H, $\text{C}(\text{CH}_3)_3$ Boc).

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3): δ 171.5 (C-4), 154.4 (C=O, Boc), 74.8 (C-6), 53.5 (C-7a), 46.4 (C-2), 43.1 (C-3a), 33.4 (C-8), 29.5 (C-3), 28.6 (4C, $\text{C}(\text{CH}_3)_3$ Boc, C-7), 28.0 ($\text{C}(\text{CH}_3)_3$ Boc).

FTIR (KBr) ν_{max} : 3449, 2960, 2926, 2854, 2097, 1739, 1694, 1394, 1367, 1260, 1168, 1115, 1042 cm^{-1} .

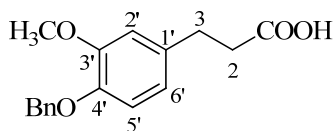
HRMS-ESI (m/z): calcd for $\text{C}_{13}\text{H}_{24}\text{N}_2\text{O}_4\text{Br}$ $[\text{M}+\text{NH}_4]^+$: 351.0903, found: 351.0927

$[\alpha]_{\text{D}}$ = - 96.1 ($c = 0.71$, CHCl_3)

Mp: 90-92°C

Synthesis of 3-(4-Benzoyloxy-3-methoxyphenyl)propionic acid (**192**).

A solution of 3-(4-hydroxy-3-methoxyphenyl)propanoic acid (1.0 g, 5.1 mmol), benzyl bromide (3.0 mL, 25.2 mmol), and potassium carbonate (2.0 g, 14.5 mmol) in acetone (15 mL) and acetonitrile (15 mL) was refluxed for 15 hours. The reaction mixture was concentrated in vacuo. To the residue was added methanol (3 mL), water (30 mL) and potassium hydroxide (4.0 g, 71 mmol). The mixture was heated at 70°C for 10 hours. After cooling to room temperature, the reaction mixture was washed with chloroform (3 X 30 mL) and concentrated hydrochloric acid (HCl) was added dropwise until the pH of the solution was 2.0. The mixture was extracted with chloroform (3 X 40 mL) and the organic layer was washed with water and brine, dried over MgSO_4 , and evaporated in vacuo to obtain **192** as beige solid (1.1 mg, 75%) that was used without further purification.



$^1\text{H-NMR}$ (300 MHz, CD_3OD): δ 7.49-7.29 (m, 5H, Ar-H OBn), 6.789 (d, 1H, $J_{5',6'} = 8.1$ Hz, H-5'), 6.87 (s, 1H, H-2'), 6.72 (dd, 1H, $J_{6',5'} = 8.1$, $J_{6',2'} = 1.8$ Hz, H-6'), 5.06 (s, 2H, $-\text{OCH}_2\text{Ph}$), 3.84 (s, 3H, OCH_3), 2.86 (t, 2H, $J_{2,3} = 7.0$ Hz, 2H-2), 2.57 (t, 2H, $J_{3,2} = 7.0$ Hz, 2H-3).

$^{13}\text{C-NMR}$ (75 MHz, CD_3OD): δ 177.1 (CO_2H), 151.5 (C-3'), 148.2 (C-4'), 139.2 (Ar-C, OBn), 136.2 (Ar-C, OBn), 129.7 (2C, Ar-C, OBn), 129.1 (C-1'), 129.0 (2C, Ar-C, OBn), 121.8 (C-6'), 116.4 (C-5'), 114.2 (C-2'), 72.8 ($-\text{OCH}_2\text{Ph}$), 56.8 (OCH_3), 37.2 (C-2), 31.9 (C-3).

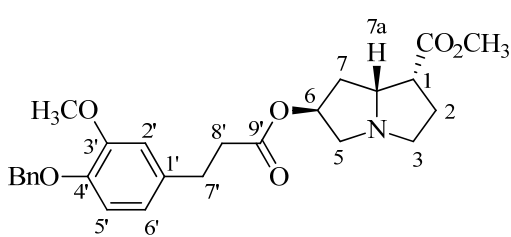
FTIR (KBr) ν_{\max} : 3436, 2928, 1703, 1518, 1462, 1430, 1253, 1235, 1210, 1143, 1033, 1012, 809 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{17}\text{H}_{18}\text{O}_4$ $[\text{M}+\text{H}]^+$: 286.1205, found: 286.1218

Mp: 95-97°C

Synthesis of (1R,6S,7aR)-methyl 6-{{3-(4-(benzyloxy)-3-methoxyphenyl)propanoyl}oxy}hexahydro-1H-pyrrolizine-1-carboxylate (193).

Bromide **189** (50 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (5 mL) and TFA (0.5 mL) was added dropwise. The reaction mixture was stirred for 1 hour and 30 minutes and then the solvent was removed in vacuo. The crude amine was then dissolved in MeOH (5 mL) and a freshly prepared NaOMe solution in methanol was added. The reaction was stirred for one hour at room temperature and the methanol was eliminated under reduced pressure. The crude was dissolved in HCl (5%) and extracted with ether (10 mL) once. The aqueous layer was basified with NaOH (1N) and extracted with CH_2Cl_2 (3 X 30 mL). The combined organic layer were dried with MgSO_4 , filtered and concentrated in vacuo to obtain the hydroxy ester **191** that was used without further purification. To a solution of crude hydroxy ester in CH_2Cl_2 (4 mL), benzyloxy-protected hydroferulic acid **192** (44 mg, 0.15 mmol), DMAP (0.26 mg, 0.002 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (33 mg, 0.21 mmol) were sequentially added. The reaction mixture was stirred for 3 hours at room temperature and then filtered over Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, gradient from CH_2Cl_2 to 98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford **193** (34 mg, 50%) as a white solid.



$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.41 (m, 2H, Ar-H OBn), 7.33 (m, 2H, Ar-H OBn), 7.27 (m, 1H, Ar-H OBn), 6.77 (d, 1H, $J_{5',6'} = 8.0$ Hz, H-5'), 6.73 (d, 1H, $J_{2',6'} = 2.0$ Hz, H-2'), 6.64 (m, 1H, H-6'), 5.33 (t, 1H, $J_{6,7\beta} = 5.0$ Hz, H-6), 5.10 (s, 2H, $-\text{OCH}_2\text{Ph}$), 4.14 (m, 1H, H-7a), 3.84 (s, 3H, OCH_3), 3.68 (s, 3H, CO_2CH_3), 3.36 (d, 1H, $J_{5\beta,5\alpha} = 12.1$ Hz, H-5 β), 3.26-3.17 (m, 2H, H-1 and H-3 β), 2.88-2.78 (m, 4H, H-5 α , 2H-7' and H-3 α), 2.60 (td, 2H, $J_{8',7'} = 8.0$, $J = 2.7$ Hz, 2H-8'), 2.14 (m, 1H, H-2 α), 2.05 (m, 1H, H-2 β), 1.95 (dd, 1H, $J_{7\beta,7\alpha} = 14.2$, $J_{7\beta,7a} = 7.0$ Hz, H-7 β), 1.72 (ddd, 1H, $J_{7\alpha,7\beta} = 14.2$, $J_{7\alpha,7a} = 10.0$, $J_{7\alpha,6} = 5.0$ Hz, H-7 α).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 172.9 (CO_2CH_3), 172.5 (C-9'), 149.5 (C-4'), 146.6 (C-3'), 137.2 (Ar-C, OBn), 133.5 (C-1'), 128.4 (2C, Ar-C, OBn), 127.7 (Ar-C, OBn), 127.2 (2C, Ar-C,

OBn), 120.0 (C-6'), 114.1 (C-5'), 112.1 (C-2'), 75.7 (C-6), 71.1 (-OCH₂Ph), 64.2 (C-7a), 59.7 (C-5), 55.9 (OCH₃), 53.2 (C-3), 51.9 (CO₂CH₃), 46.2 (C-1), 36.0 (C-8'), 34.1 (C-7), 30.3 (C-7'), 27.1 (C-2).

FTIR (KBr) ν_{max} : 3062, 3033, 2951, 2871, 1732, 1606, 1591, 1463, 1455, 1419, 1378, 1262, 1231, 1158, 1139, 1034, 853, 807, 736, 698 cm⁻¹.

HRMS-ESI (m/z): calcd for C₂₆H₃₂NO₆ [M+H]⁺: 454.2240, found: 454.2234

[α]_D = - 3.8 (c = 1.75, CHCl₃)

Mp: 101-103°C

Catalytic hydrogenation. Synthesis of (1*R*,6*S*,7*aR*)-methyl 6-{[3-(4-hydroxy-3-methoxyphenyl)propanoyl]oxy}hexahydro-1*H*-pyrrolizine-1-carboxylate (194, Amforogynine C).

Activated Pd/C (10%, 4 mg) was added in a single portion to a solution of **193** (35 mg, 0.077 mmol) in EtOAc (3 mL). The mixture was stirred under H₂ atmosphere for 2 hours. Upon completion, the reaction was filtered through Celite using several washes of EtOAc to ensure quantitative transfer. The solvent was removed under reduce pressure and the crude was purified by column chromatography (silica gel, gradient from CH₂Cl₂ to 97:3 CH₂Cl₂/MeOH) to obtain amforogynine C (21 mg, 75%) as a white solid. The relative stereochemistry of amforogynine C was confirmed by X-ray crystallographic.⁴

¹H-NMR (400 MHz, CDCl₃): δ 6.80 (d, 1H, $J_{5',6'} = 8.0$ Hz, H-5'), 6.68 (d, 1H, $J_{2',6'} = 1.9$ Hz, H-2'), 6.65 (dd, 1H, $J_{6',5'} = 8.0$, $J_{6',2'} = 1.9$ Hz, H-6'), 5.34 (t, 1H, $J = 4.6$ Hz, H-6), 4.03 (m, 1H, H-7a), 3.85 (s, 3H, OCH₃), 3.69 (s, 3H, CO₂CH₃), 3.28 (d, 1H, $J_{5\beta,5\alpha} = 11.8$ Hz, H-5 β), 3.19 (ddd, 1H, $J = 8.2$, $J = 8.2$, $J = 8.2$ Hz, H-1), 3.13 (m, 1H, H-3 β), 2.87 (m, 1H, H-5 α), 2.85 (m, 2H, 2H-7'), 2.80 (m, 1H, H-3 α), 2.58 (t, 2H, $J_{8',7'} = 8.5$ Hz, 2H-8'), 2.12 (m, 1H, H-2 α), 1.99 (m, 1H, H-2 β), 1.90 (dd, 1H, $J_{7\alpha,7\beta} = 14.1$, $J = 6.9$ Hz, H-7 α), 1.68 (ddd, 1H, $J_{7\beta,7\alpha} = 14.1$, $J = 9.7$, $J = 5.1$ Hz, H-7 β).

¹³C-NMR (100 MHz, CDCl₃): δ 173.5 (CO₂CH₃), 172.8 (C-9'), 144.3 (C-4'), 146.7 (C-3'), 132.3 (C-1'), 120.9 (C-6'), 114.6 (C-5'), 111.1 (C-2'), 76.3 (C-6), 64.6 (C-7a), 60.4 (C-5), 56.0 (OCH₃), 53.8 (C-3), 52.0 (CO₂CH₃), 46.7 (C-1), 36.4 (C-8'), 34.4 (C-7), 30.7 (C-7'), 27.3 (C-2).

⁴ Los datos de difracción de rayos X de la amforoginina C se encuentran en el anexo II.

FTIR (KBr) ν_{max} : 2952, 1732, 1597, 1516, 1452, 1436, 1377, 1275, 1236, 1202, 1156, 1125, 1035, 754 cm^{-1} .

HRMS-ESI (m/z): calcd for $\text{C}_{19}\text{H}_{26}\text{NO}_6$ $[\text{M}+\text{H}]^+$: 364.1755, found: 364.1765

$[\alpha]_{\text{D}}$ = - 1.7 (c = 1.30, CHCl_3)⁵

Mp: 120°C

⁵ Debido al bajo valor de $[\alpha]_{\text{D}}$ se decidió medir a diferentes longitudes de onda para comprobar. $[\alpha]_{578} = -1.9$ (c = 1.30, CHCl_3), $[\alpha]_{546} = -2.3$ (c = 1.30, CHCl_3), $[\alpha]_{465} = -1.8$ (c = 1.30, CHCl_3), $[\alpha]_{365} = -27.1$ (c = 1.30, CHCl_3)

Capítulo 5

CONCLUSIONES

De los resultados obtenidos en esta tesis doctoral y recogidos en esta memoria, se puede concluir:

- Se ha desarrollado un nuevo proceso en cascada consistente en una reacción de cicloadición 1,3-dipolar azida-alqueno intramolecular y la posterior reacción de la enamina generada a un grupo electrófilo convenientemente situado para la síntesis de heterociclos nitrogenados.

- Se ha puesto a punto una sencilla ruta de síntesis para los azido alquenos convenientemente funcionalizados empleados como sustratos en la reacción en cascada, empleando como etapa clave una reacción de Wittig.

- Se ha comprobado la generalidad de esta reacción empleando diferentes electrófilos:

- Por un lado, el uso como grupo electrófilo de cetonas y enonas cíclicas, ha permitido la preparación de manera eficiente de diferentes imino alcoholes de elevada complejidad estructural. Especialmente relevante resulta la preparación de los imino alcoholes tetracíclicos (**47**, **49**, **55** y **57**) ya que se accede a ellos a través de una triple reacción en cascada de cicloadición 1,3-dipolar azida-alqueno intramolecular/adición 1,4/adición 1,2 a través de la cual se crean en una sola etapa tres ciclos y cuatro centros estereogénicos nuevos de manera totalmente estereoselectiva. Además la adición de la enamina exocíclica sobre la enona constituye el primer ejemplo de reacción de Michael intramolecular de una imina cíclica.

- Por otro lado, el empleo de azido alquenos lineales con diferentes grupos aceptores de Michael como electrófilos en su estructura, ha permitido la preparación de una gran variedad de iminas bicíclicas con diferentes grupos funcionales en su estructura. Como grupos aceptores de Michael se han empleado, vinil fosfonatos y vinil sulfonas, así como ésteres α,β -insaturados, cetonas α,β -insaturadas y cianuros α,β -insaturados. Las estructuras obtenidas ofrecen interesantes posibilidades para la preparación de derivados más elaborados.

- Se ha demostrado además que esta reacción en cascada es altamente estereoselectiva en todos los casos, confirmándose la estereoquímica de los productos obtenidos mediante espectros NOESY y difracción de rayos X de algunos de los compuestos obtenidos (**29**, **48**, **56**). Se ha comprobado igualmente que la estereoquímica obtenida en el caso de las iminas bicíclicas no depende de la geometría de ninguno de los dobles enlaces del azido alqueno de partida.

- Ha sido posible también llevar a cabo una triple reacción en cascada de cicloadición 1,3-dipolar azida-alqueno/adición de Michael/reacción de Mannich a partir de la azido dienona

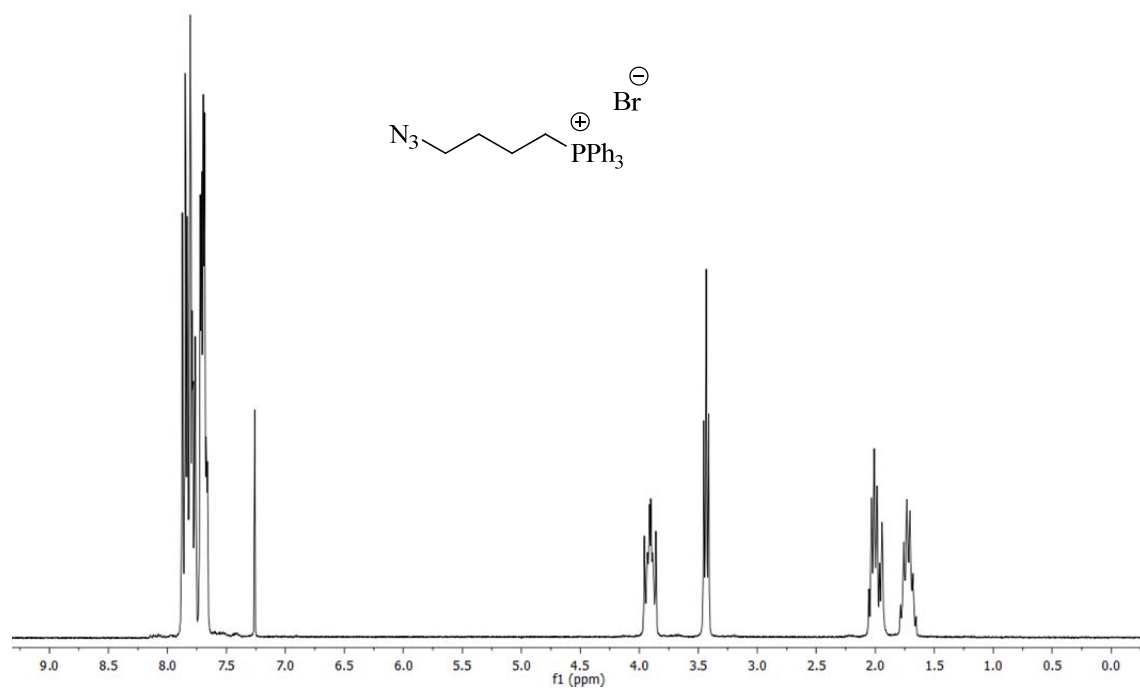
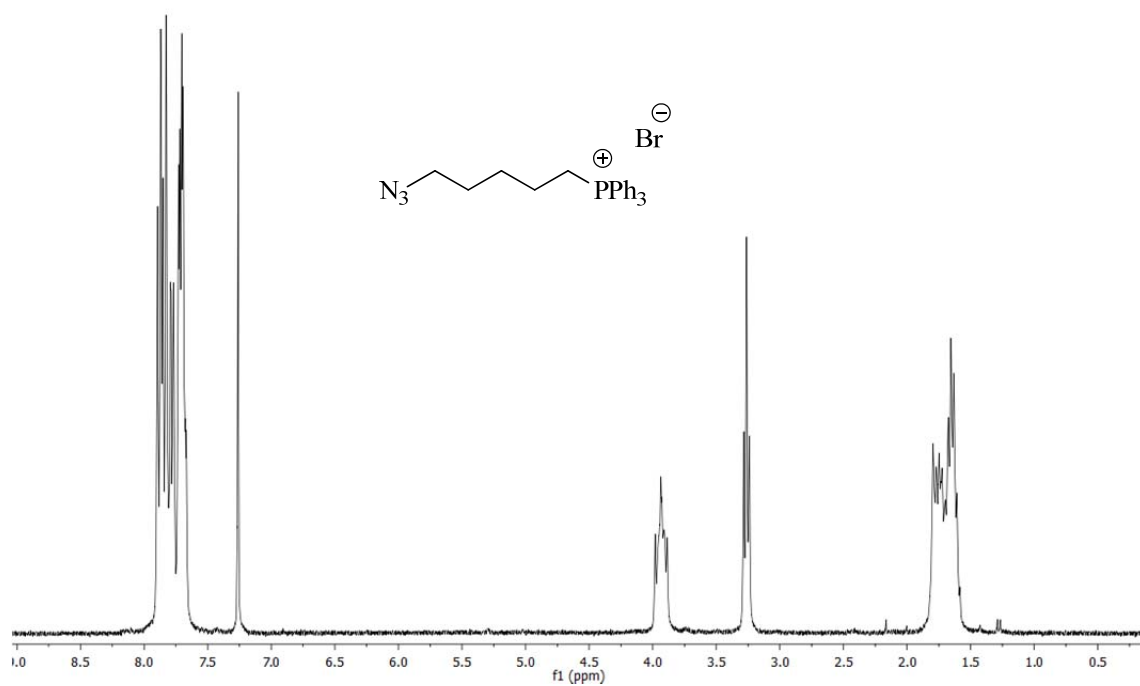
lineal (**140**), formándose en un solo paso de reacción y en tan solo 3 horas la amina tricíclica (**143**) que constituye el núcleo de varios alcaloides del género *Lycopodium*.

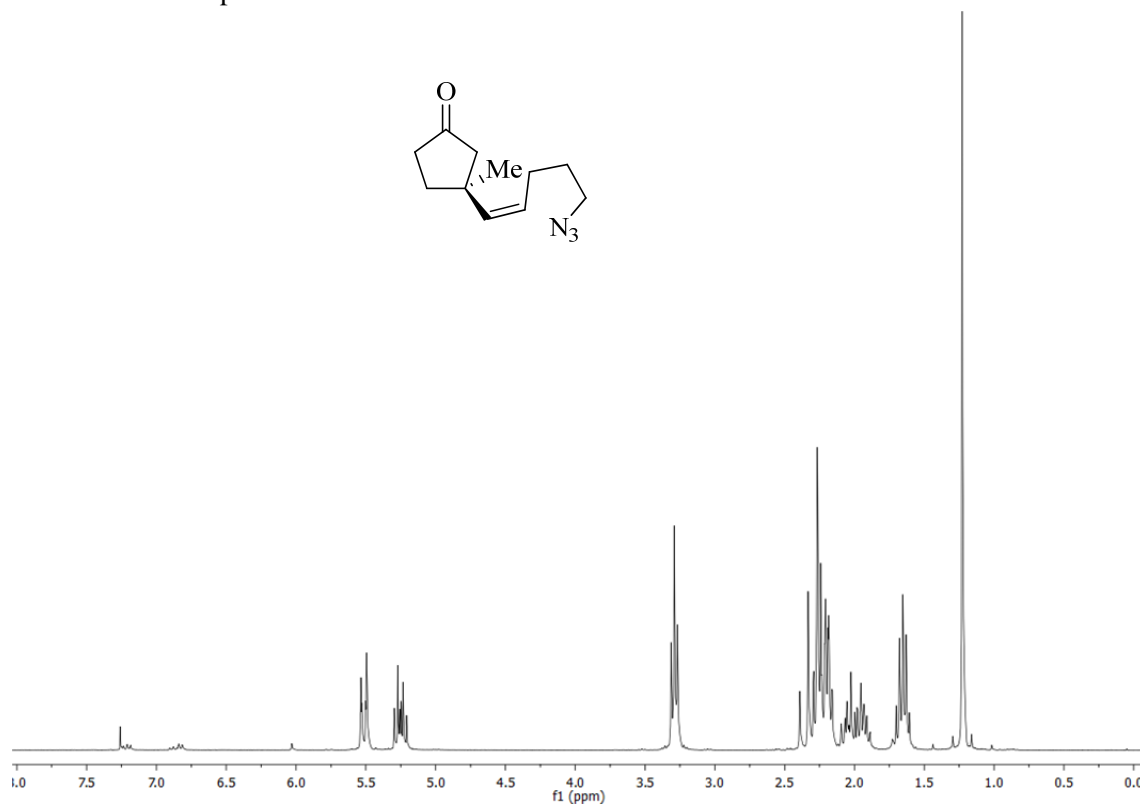
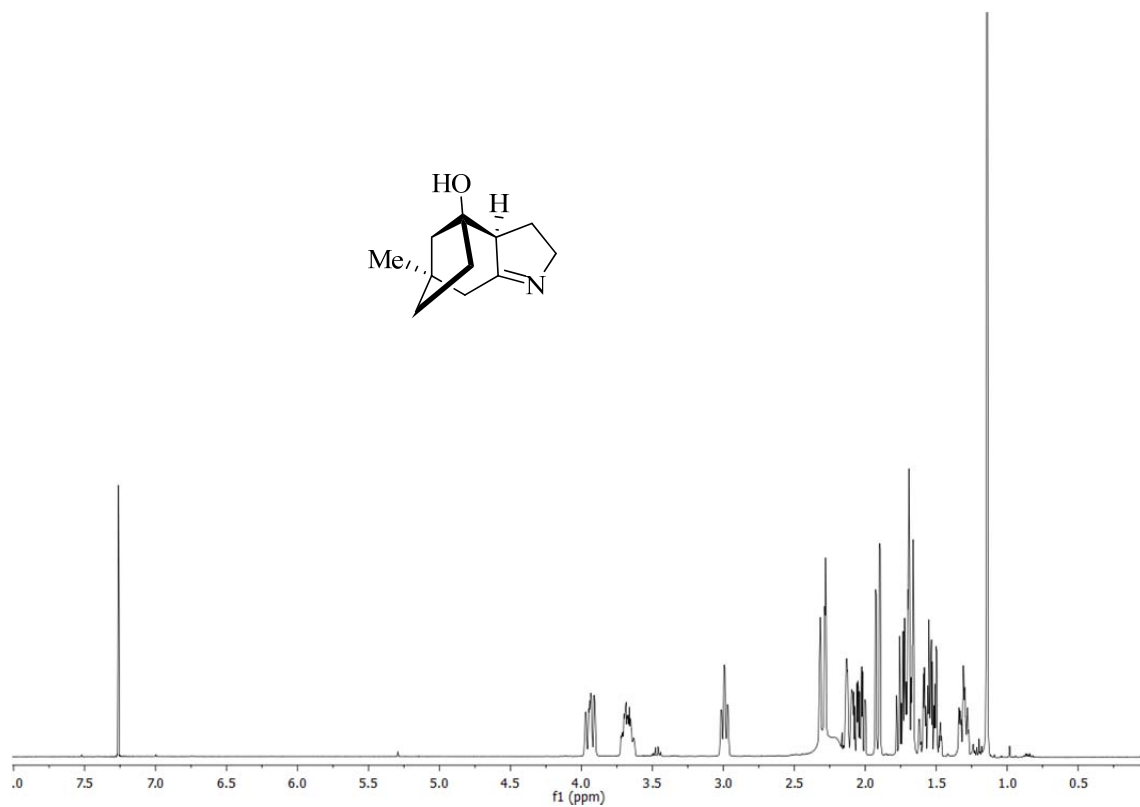
- Se ha llevado a cabo una aproximación a la síntesis total del alcaloide licopodina, inspirada en la ruta biosintética propuesta para dicho alcaloide. Dicha ruta, basada en un proceso en cascada del tipo reacción de cicloadición 1,3-dipolar azida-alqueno/adición de Michael/reacción de Mannich/*N*-alquilación, ha sido ensayada en diferentes sustratos de partida lineales. Los resultados indican que la etapa clave de adición de Michael da lugar de manera preferente al aducto de configuración no deseada, lo cual impide la posterior reacción de Mannich. Sin embargo, empleando una ruta similar se ha podido completar la síntesis de la 15-desmetil licopodina, demostrándose que la metodología desarrollada puede ser muy útil en la preparación de análogos del alcaloide licopodina, con potenciales aplicaciones terapéuticas.

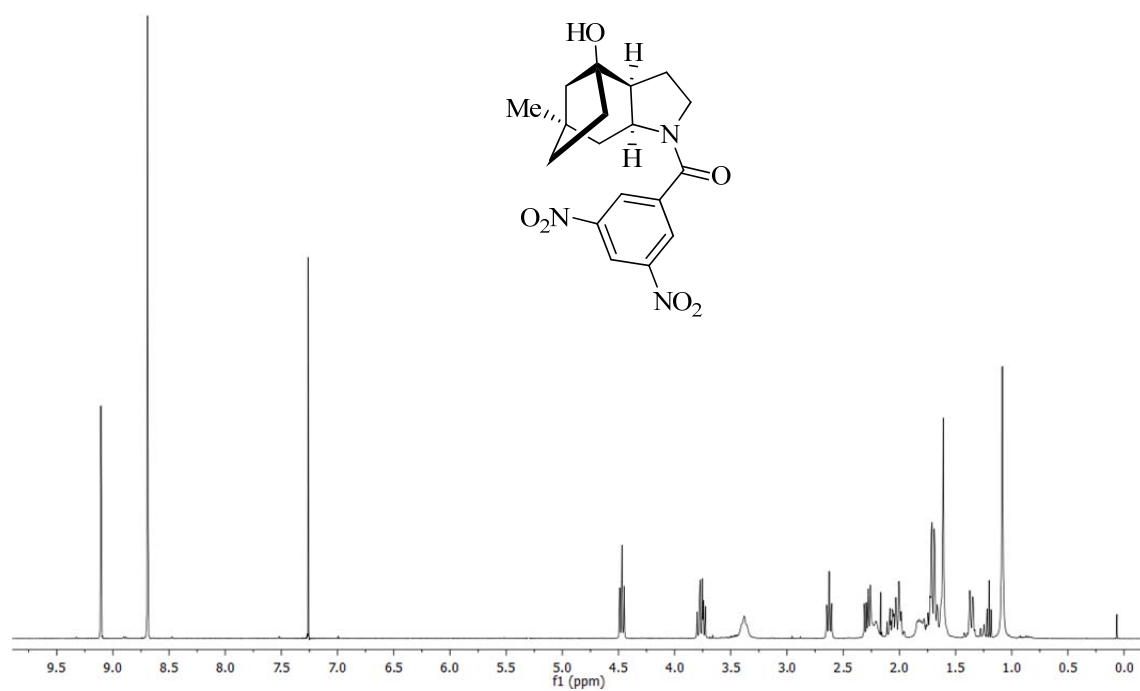
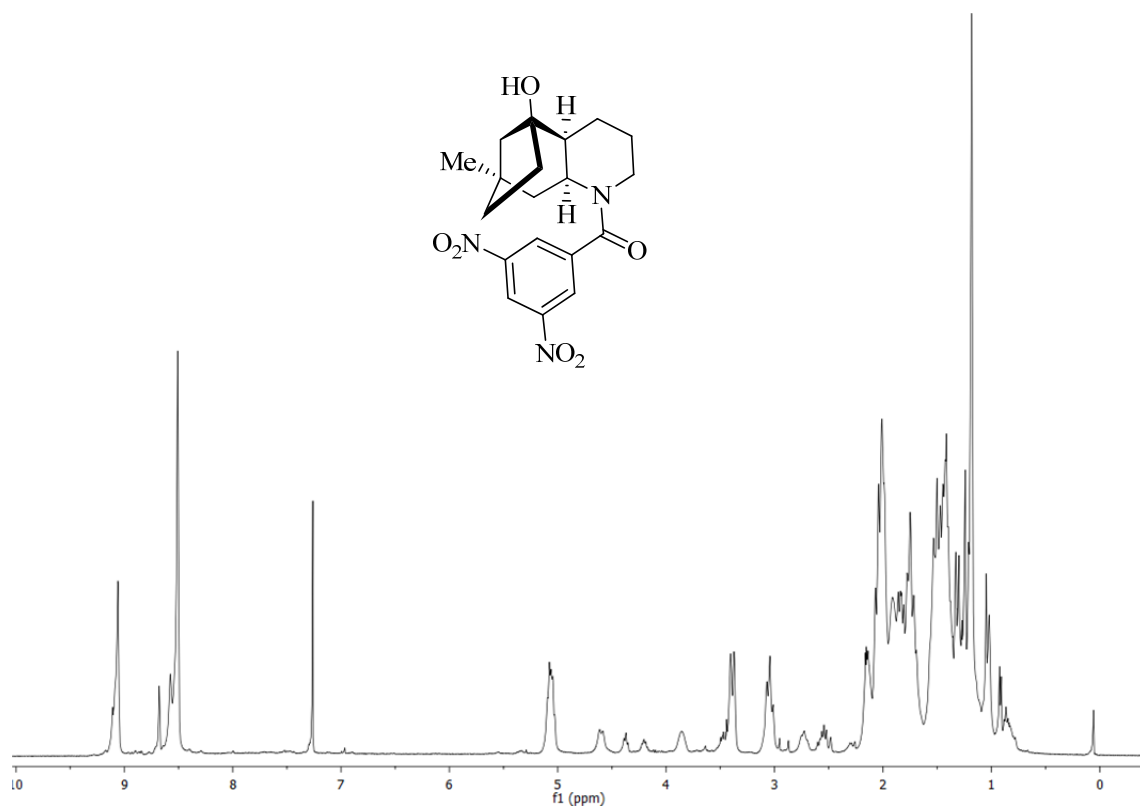
- Igualmente se ha completado la primera síntesis total de la amforoginina C de manera estereoselectiva partiendo del 3,4,6-tri-*O*-acetil-*D*-glucal en 20 etapas y con un rendimiento global del 3%. Para ello se emplearon como etapas clave una transposición de Claisen-Johnson estereoselectiva y una cicloadición 1,3-dipolar azida-alqueno intramolecular. Además se pudo cristalizar la amforoginina C y se realizó un estudio de difracción de rayos X con el que se confirmó la estructura y estereoquímica de la misma.

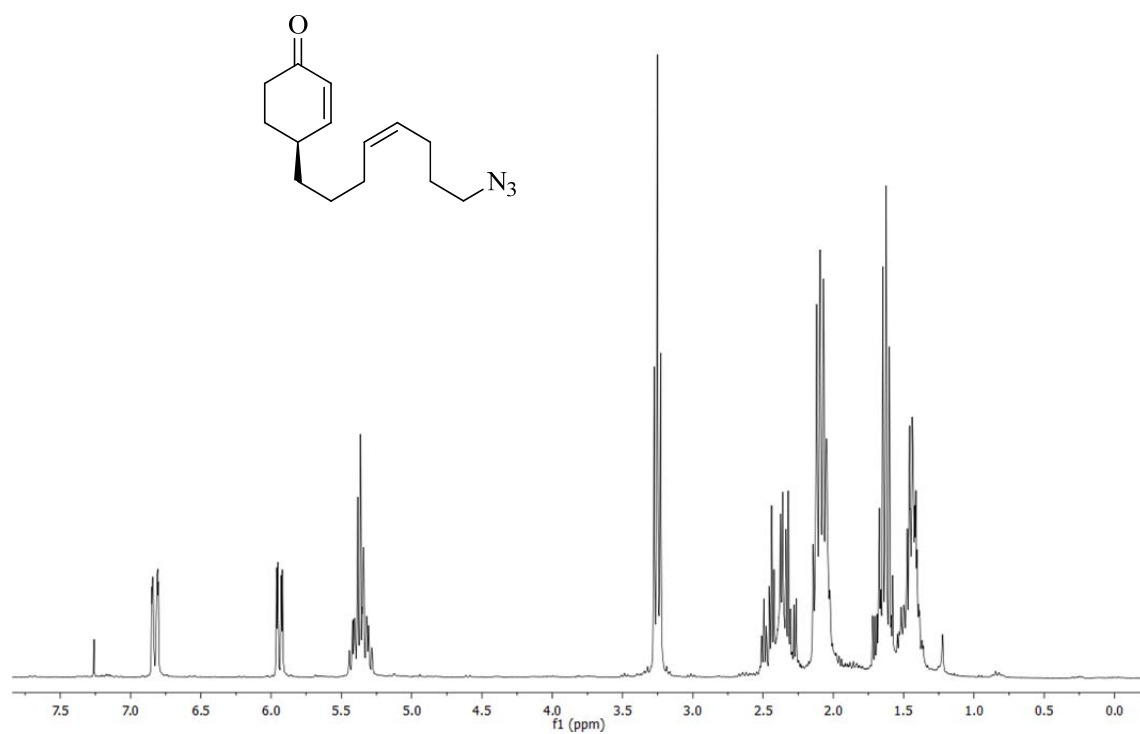
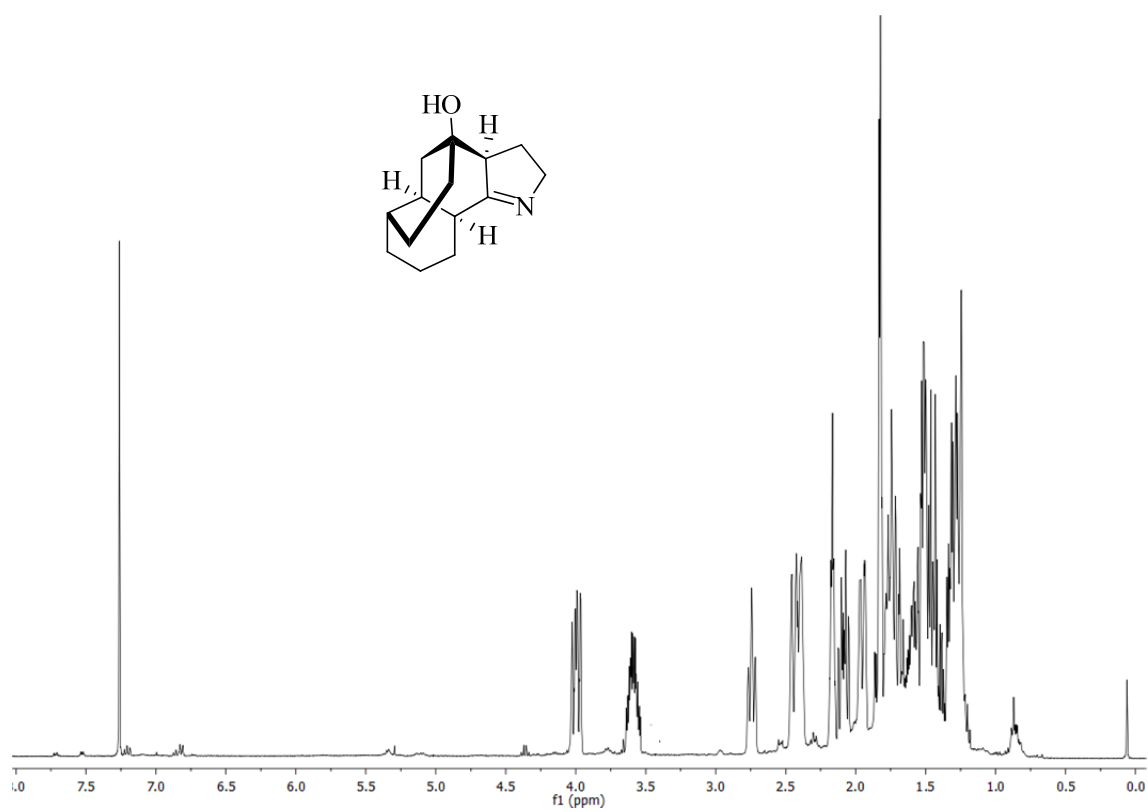
Anexo I

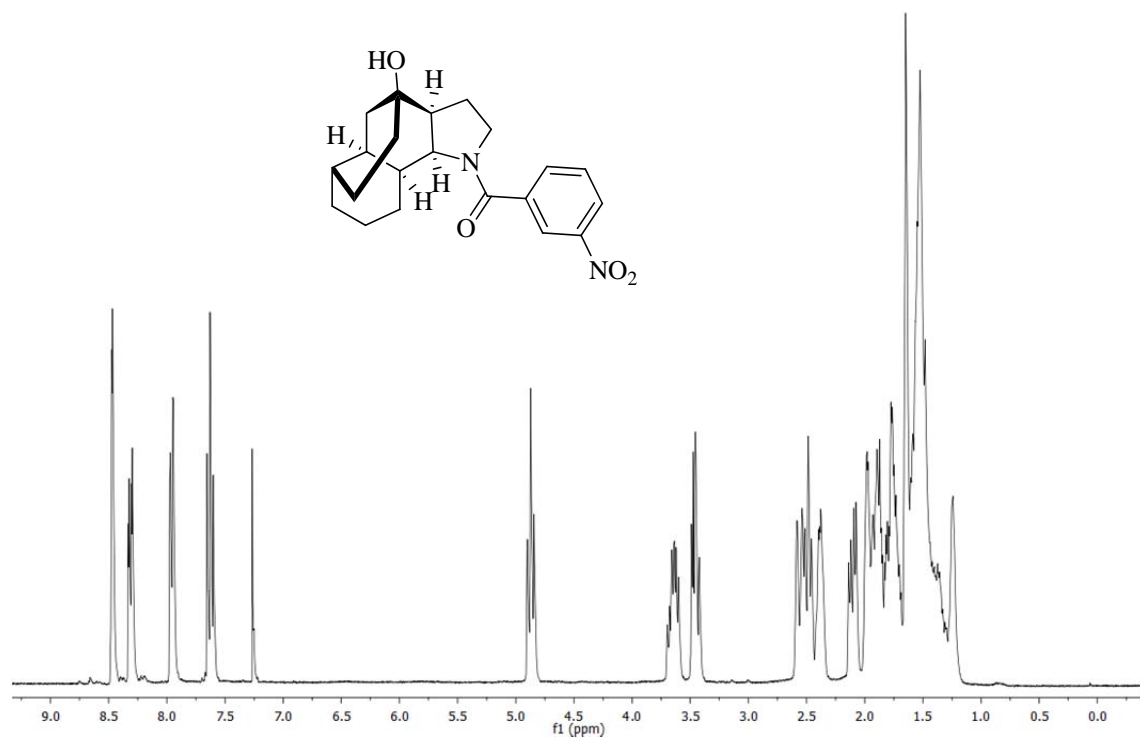
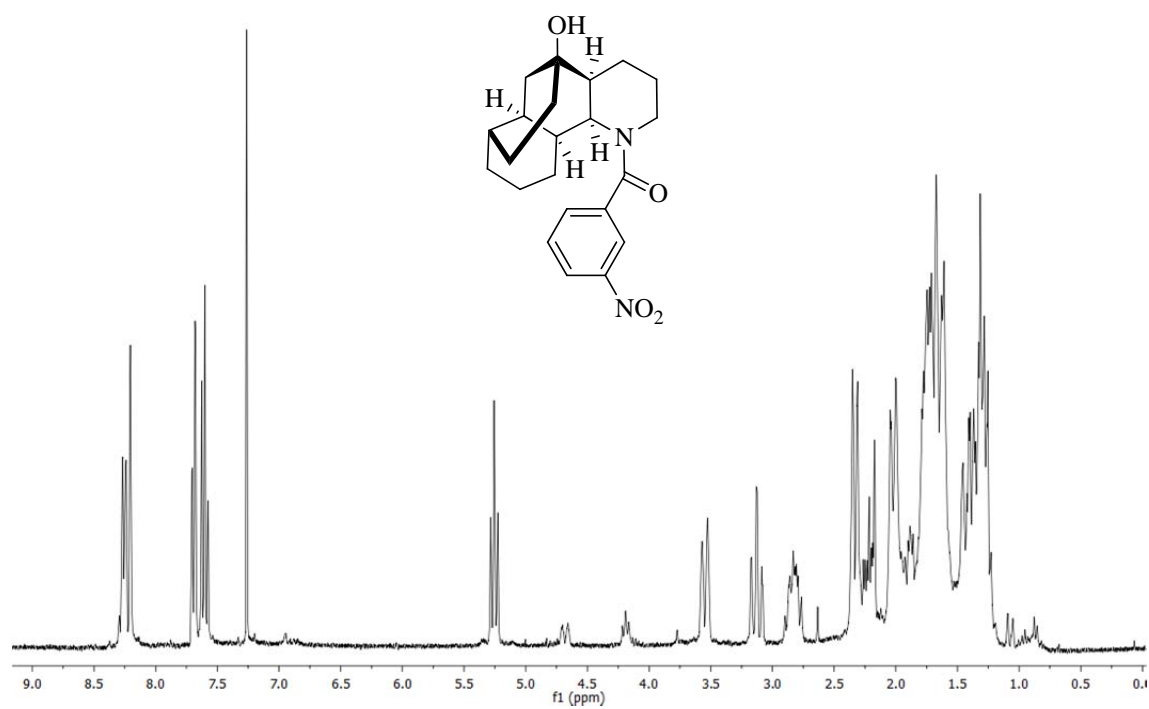
ESPECTROS DE ^1H -RMN

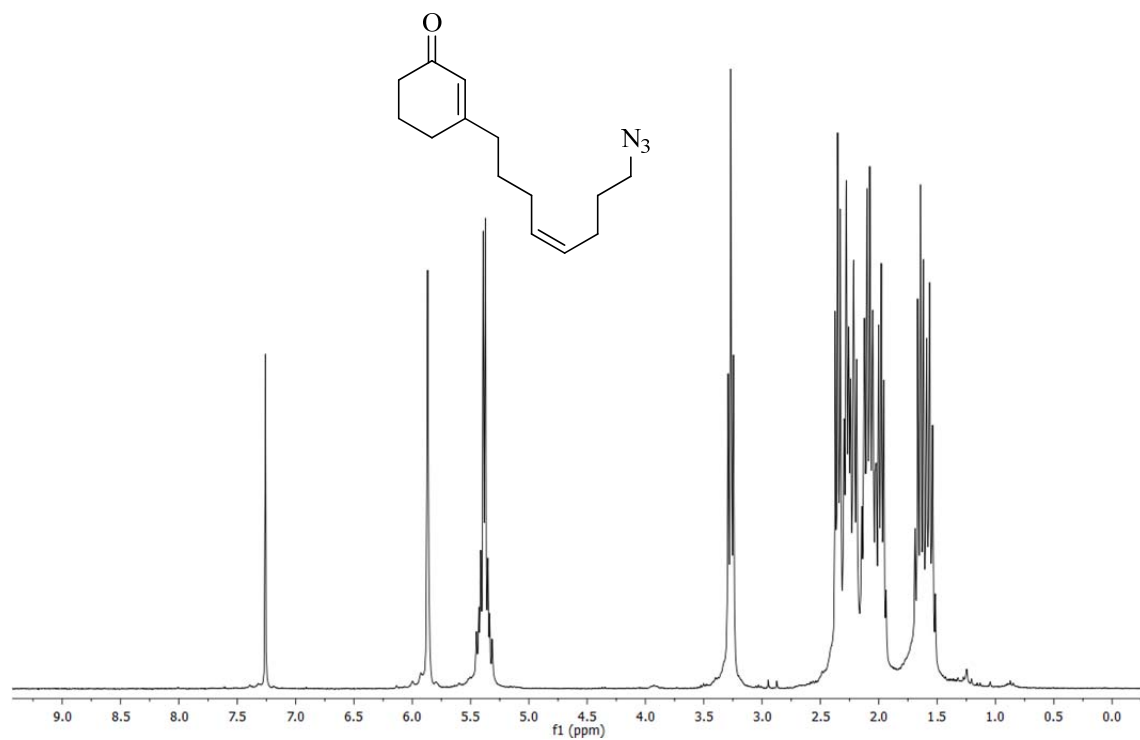
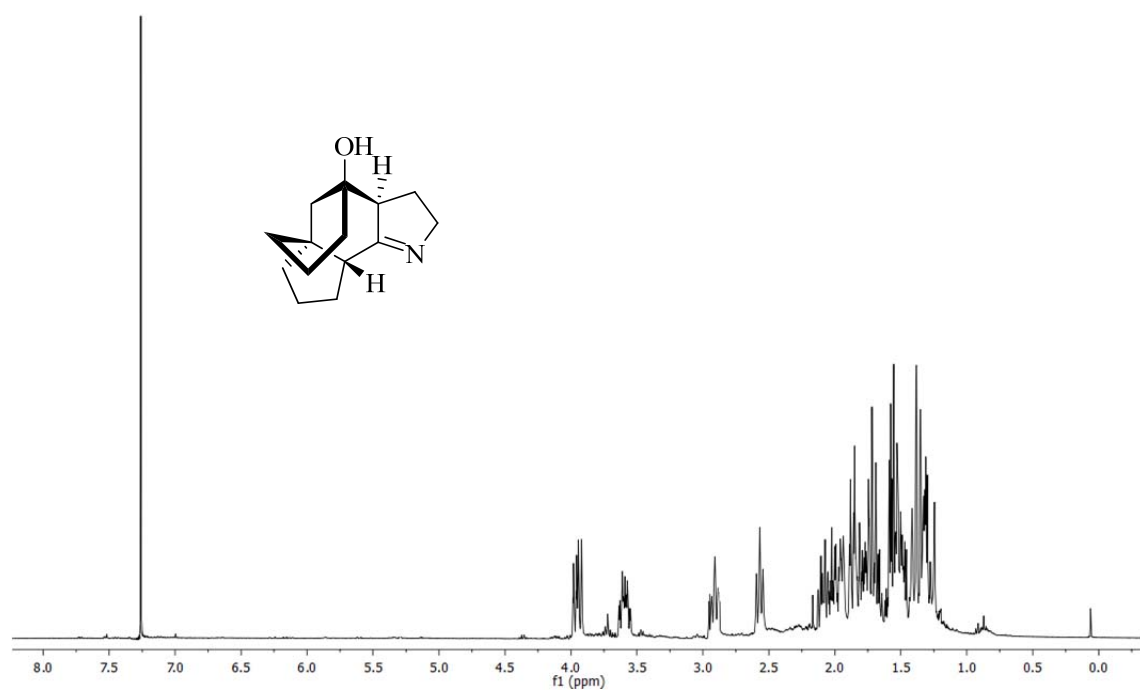
^1H -RMN del compuesto **4** ^1H -RMN del compuesto **6**

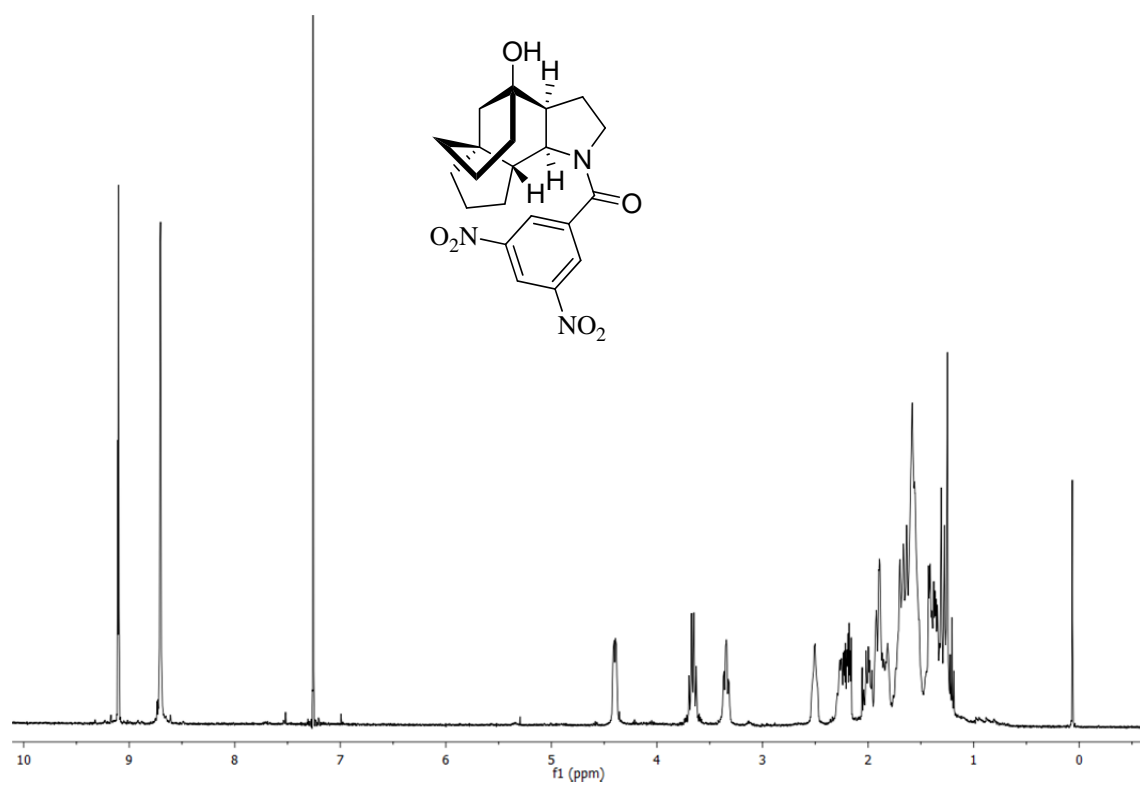
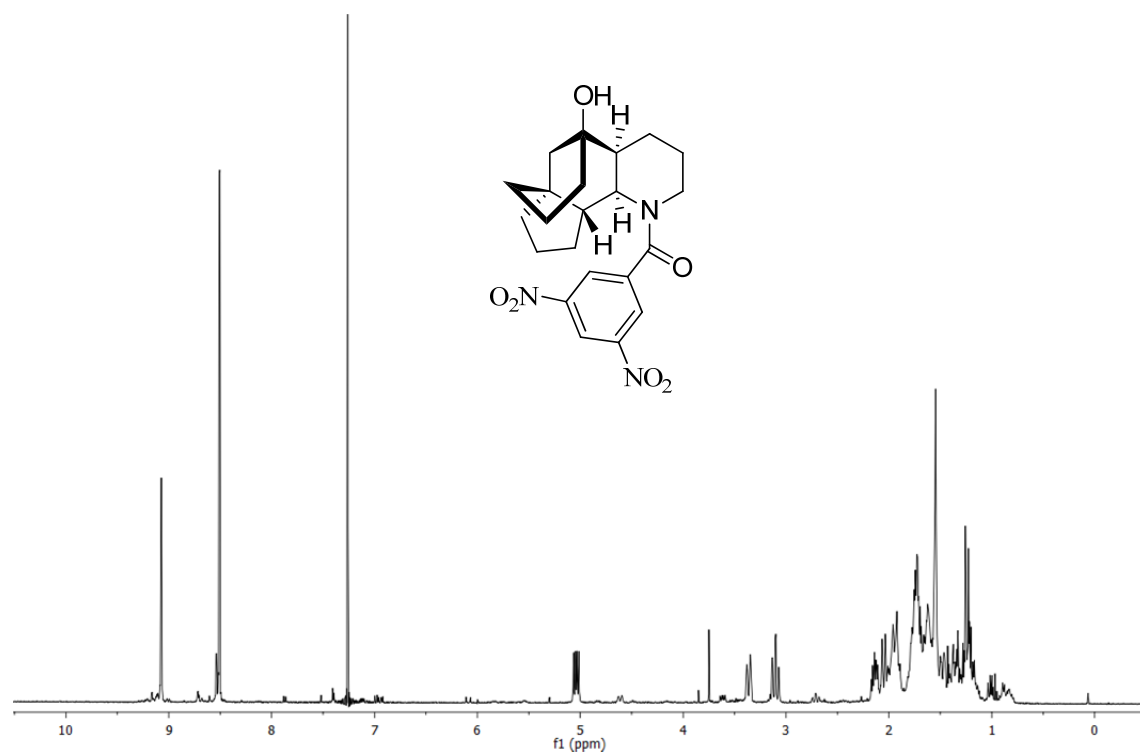
^1H -RMN del compuesto **14** ^1H -RMN del compuesto **24**

^1H -RMN del compuesto **29** ^1H -RMN del compuesto **38**

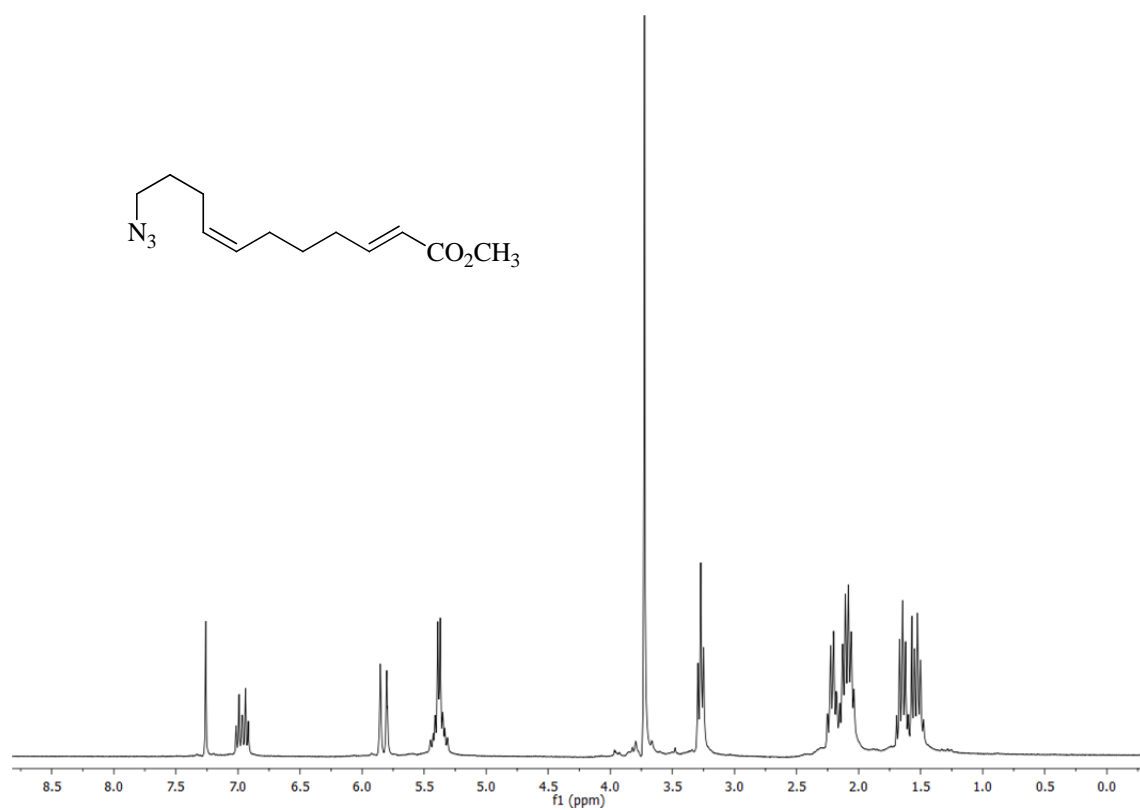
^1H -RMN del compuesto **45** ^1H -RMN del compuesto **47**

^1H -RMN del compuesto **48** ^1H -RMN del compuesto **50**

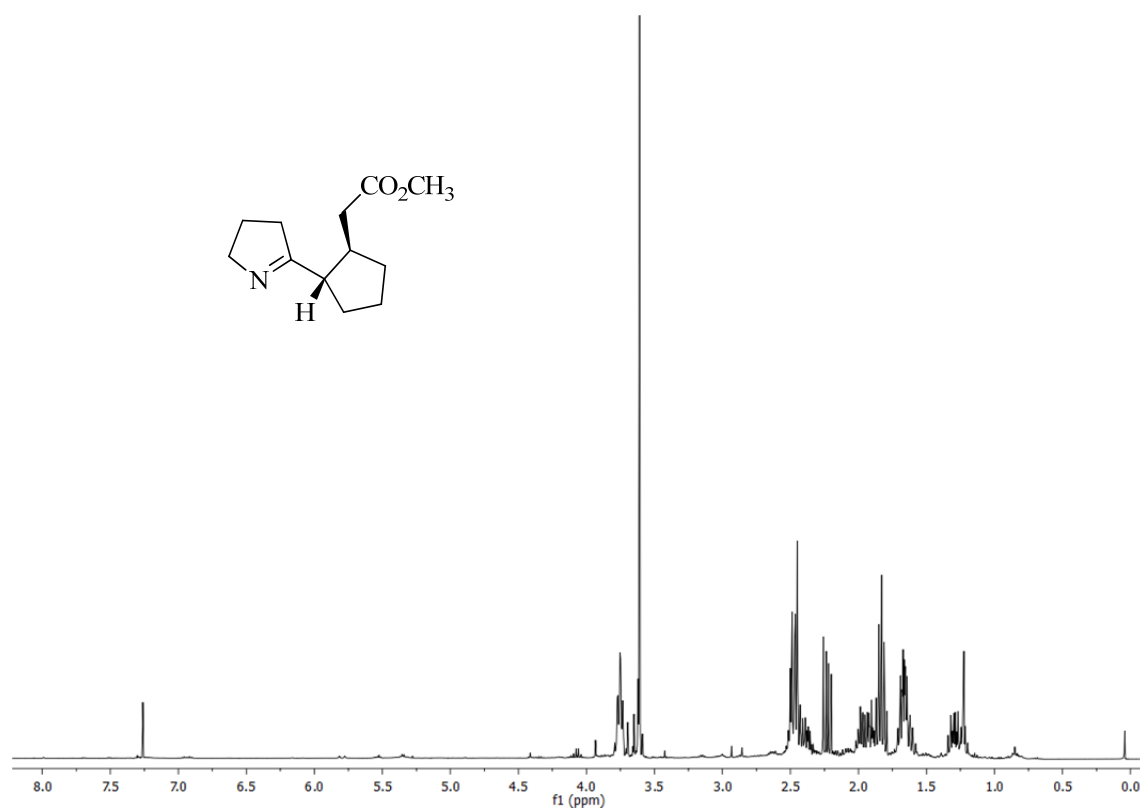
^1H -RMN del compuesto **53** ^1H -RMN del compuesto **55**

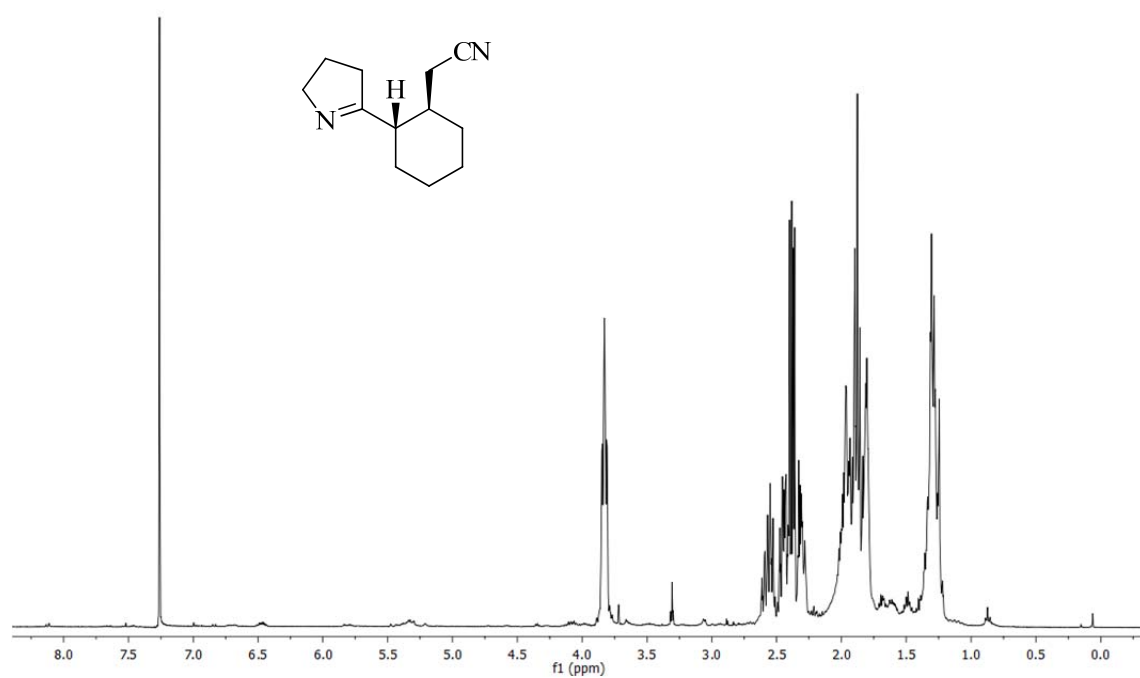
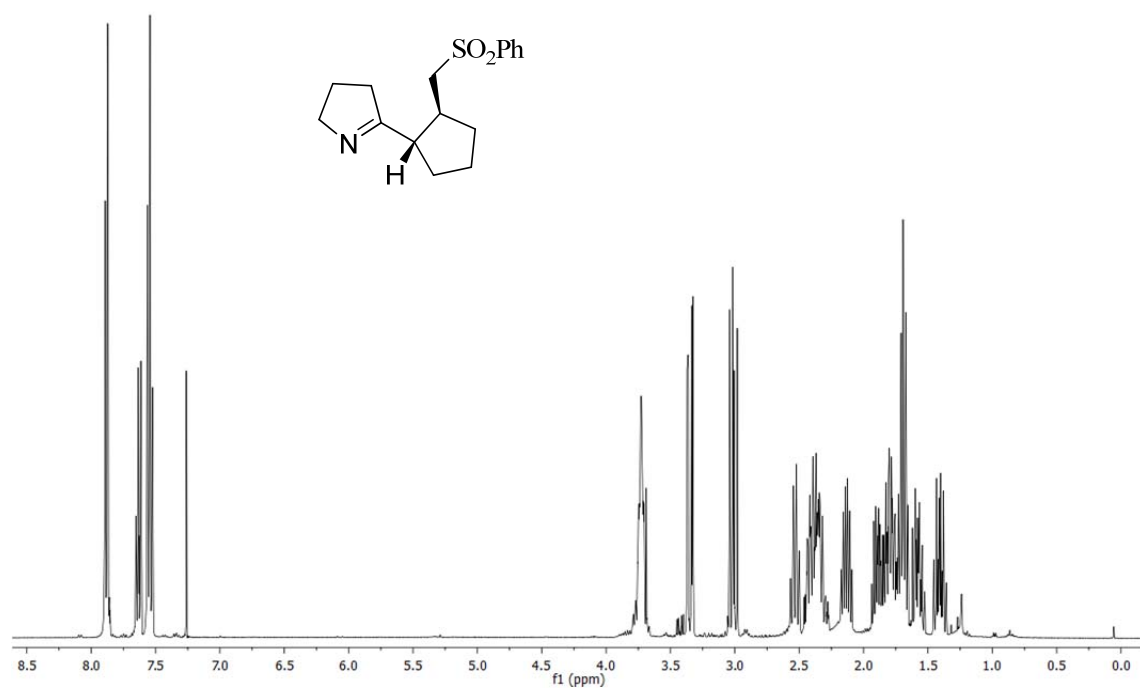
^1H -RMN del compuesto **56** ^1H -RMN del compuesto **58**

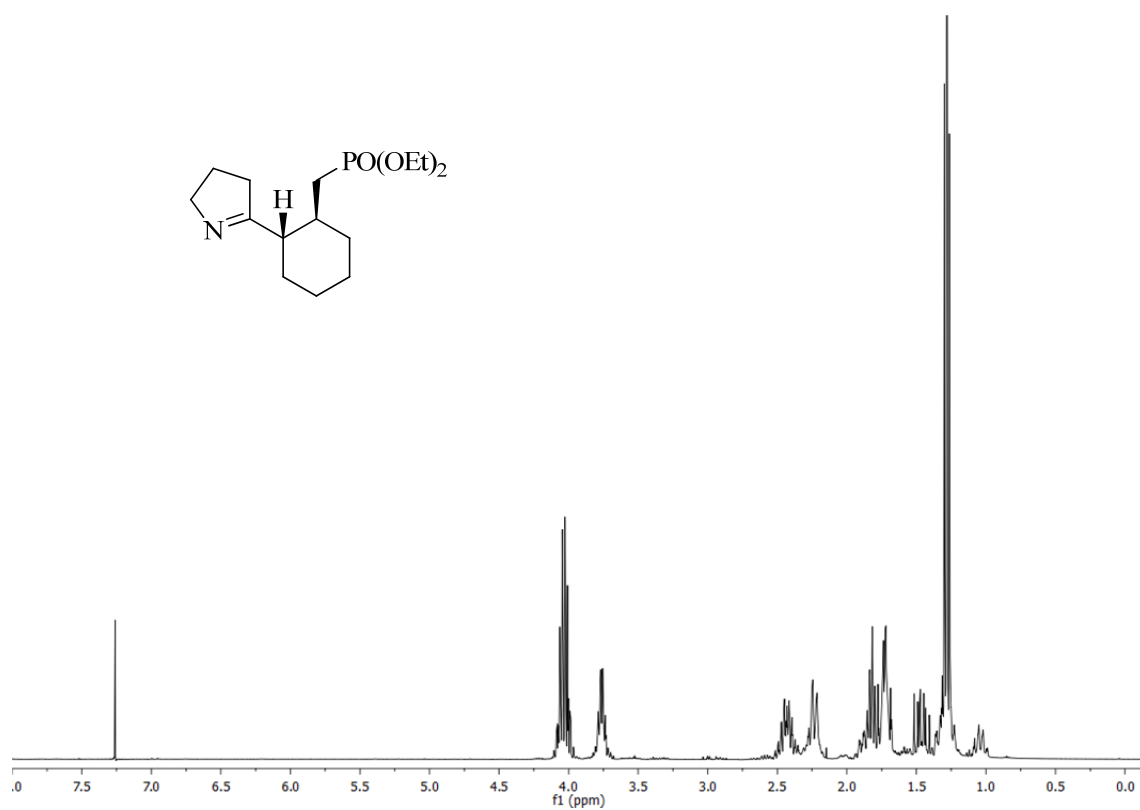
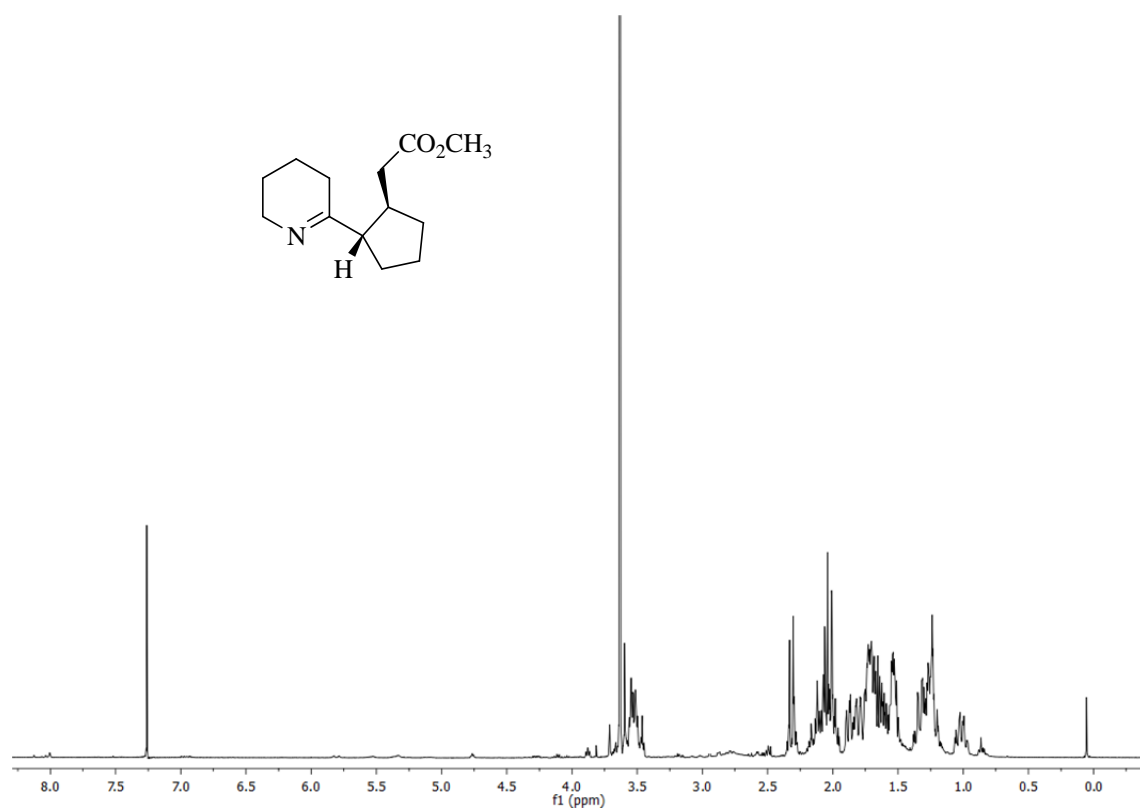
^1H -RMN del compuesto **62**

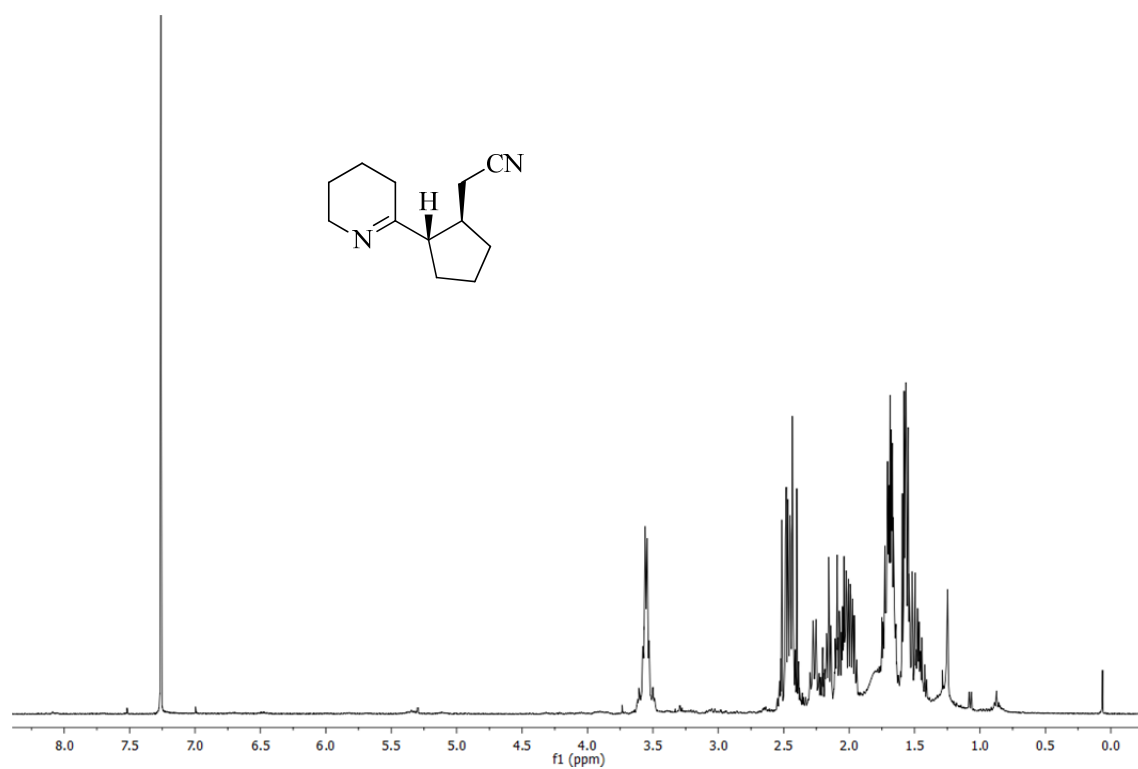
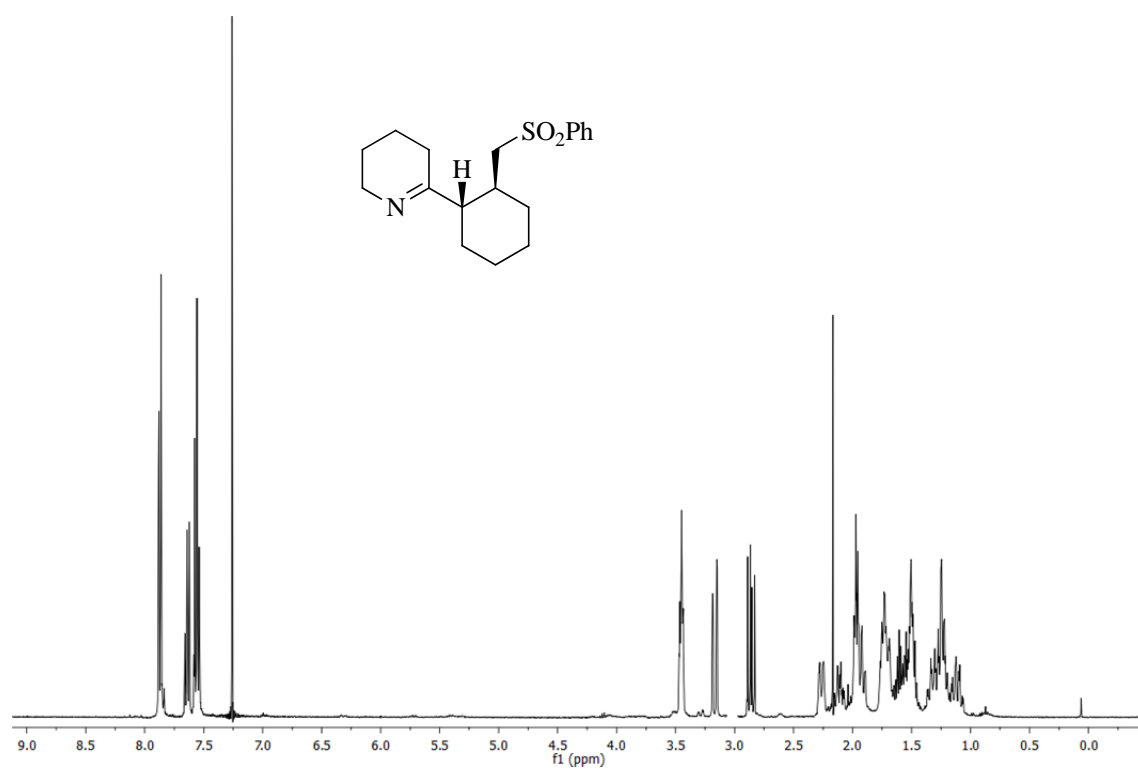


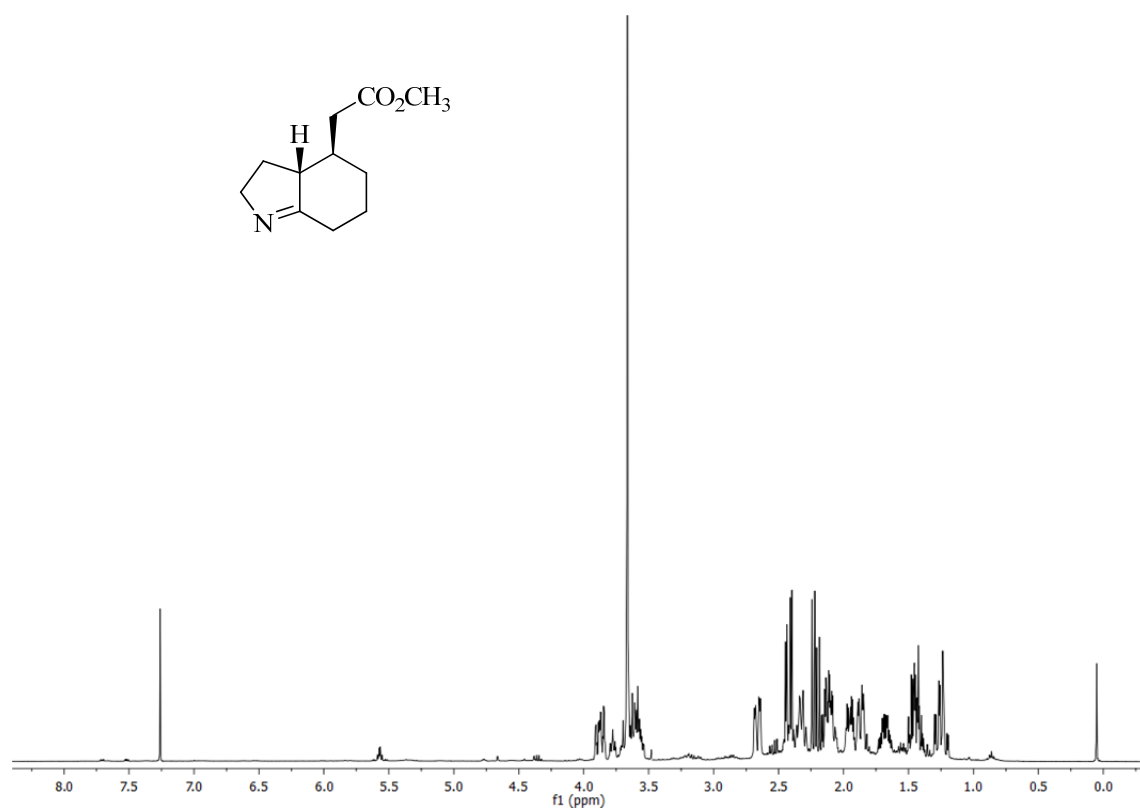
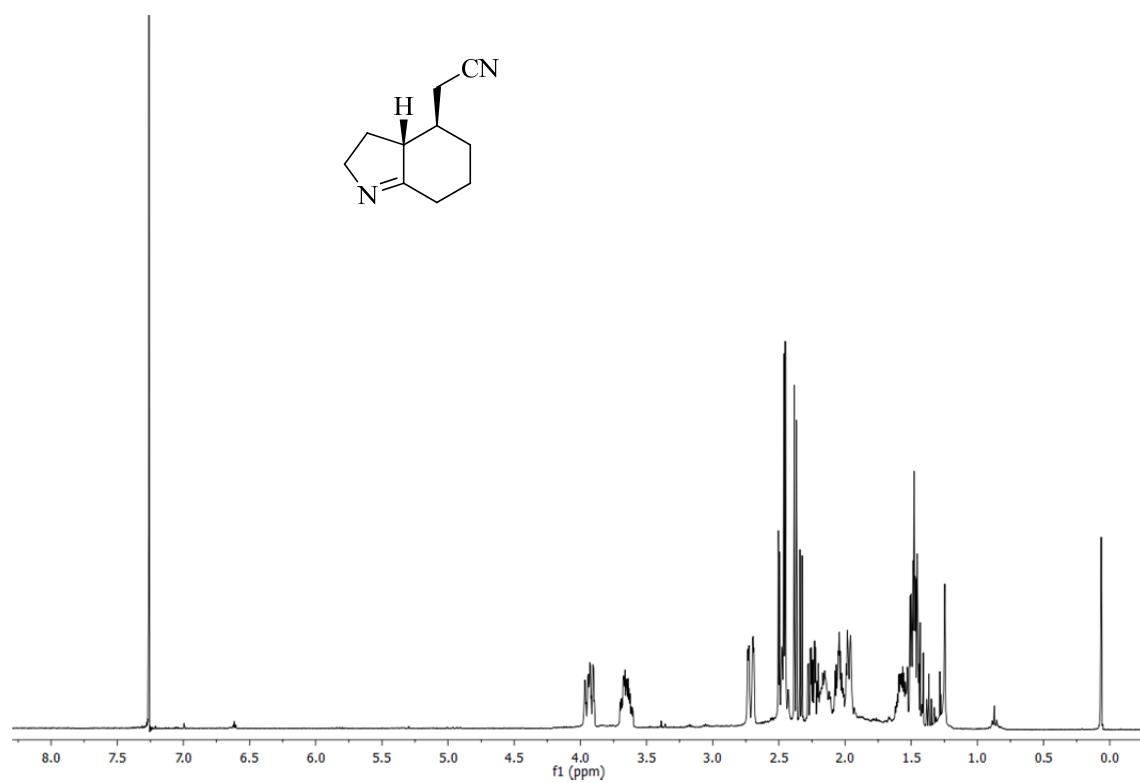
^1H -RMN del compuesto **63**

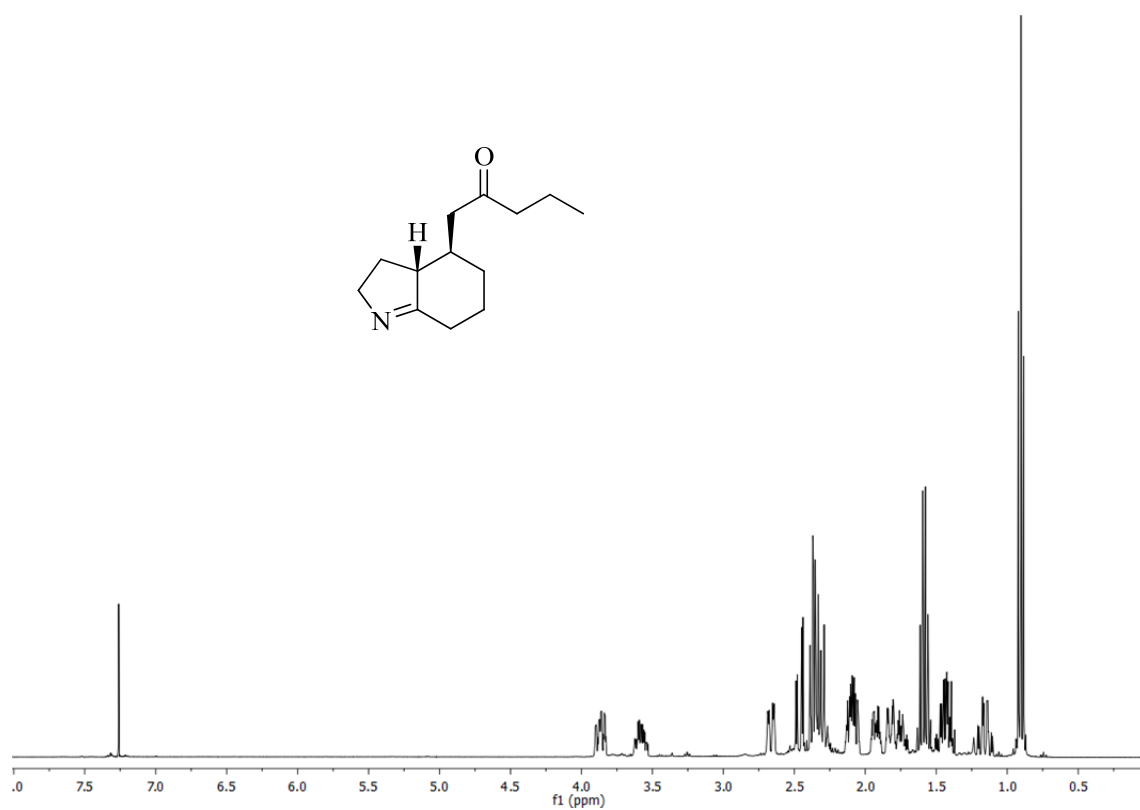
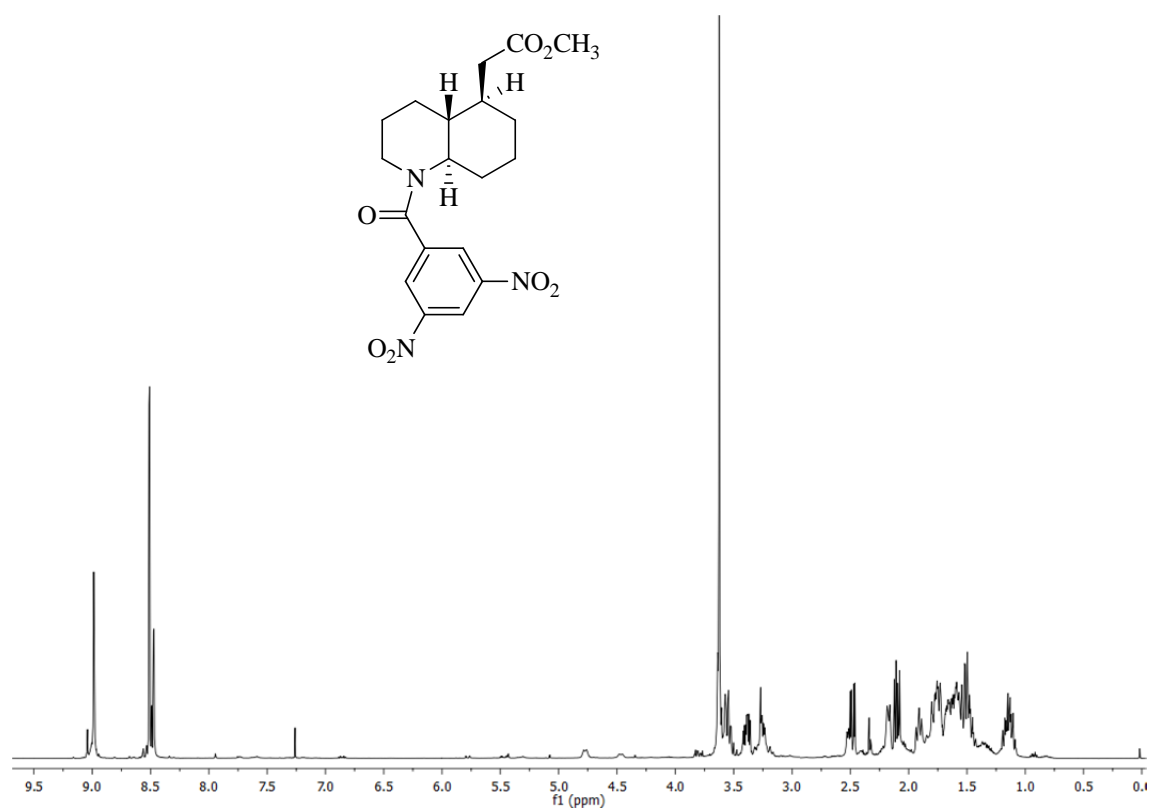


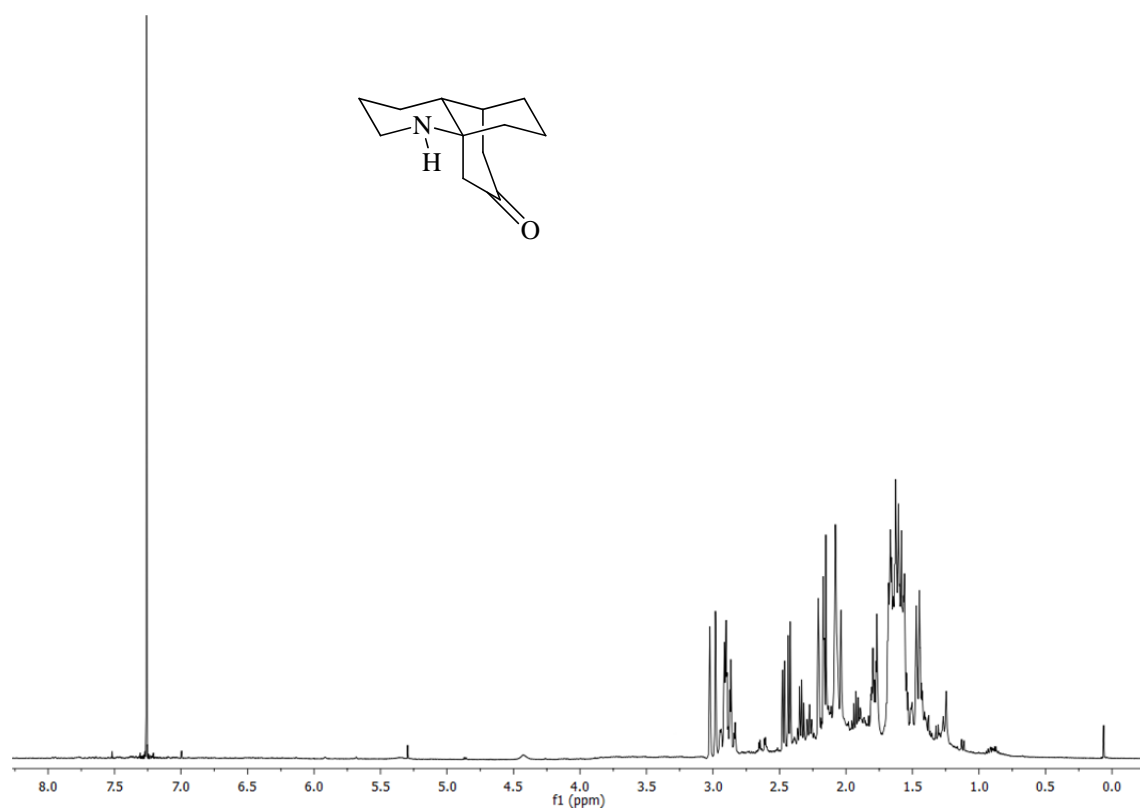
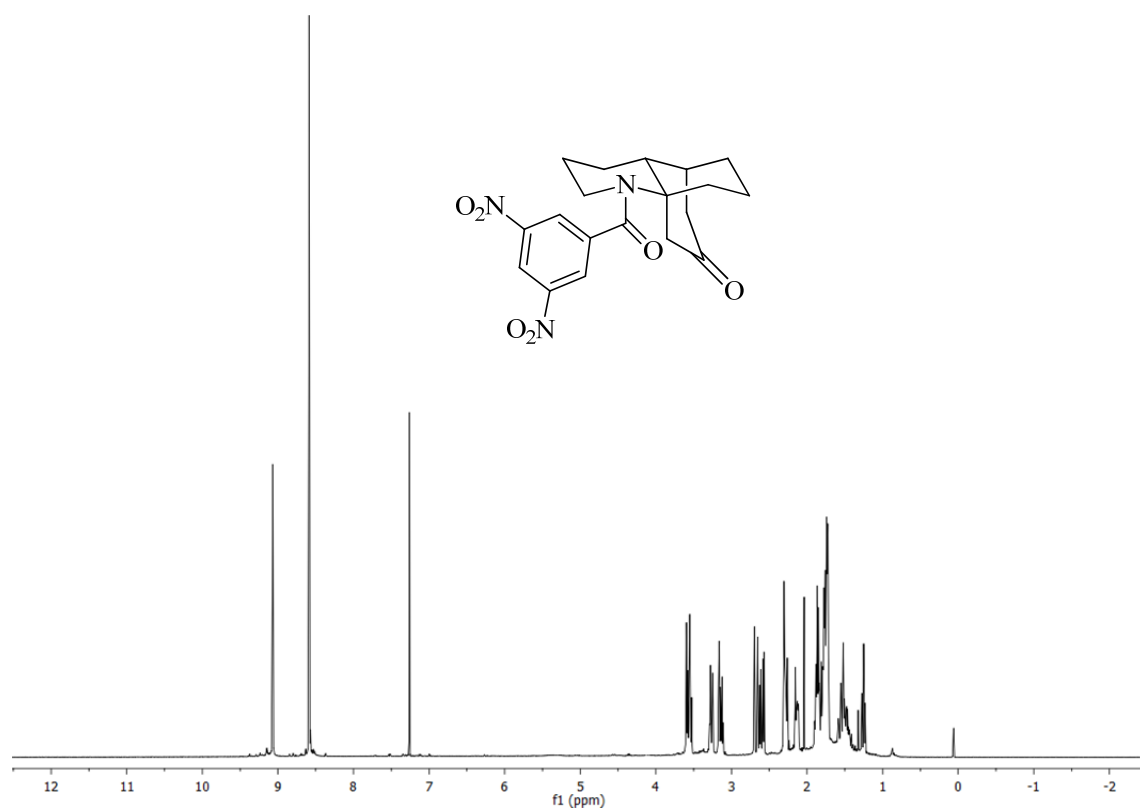
^1H -RMN del compuesto **81** ^1H -RMN del compuesto **84**

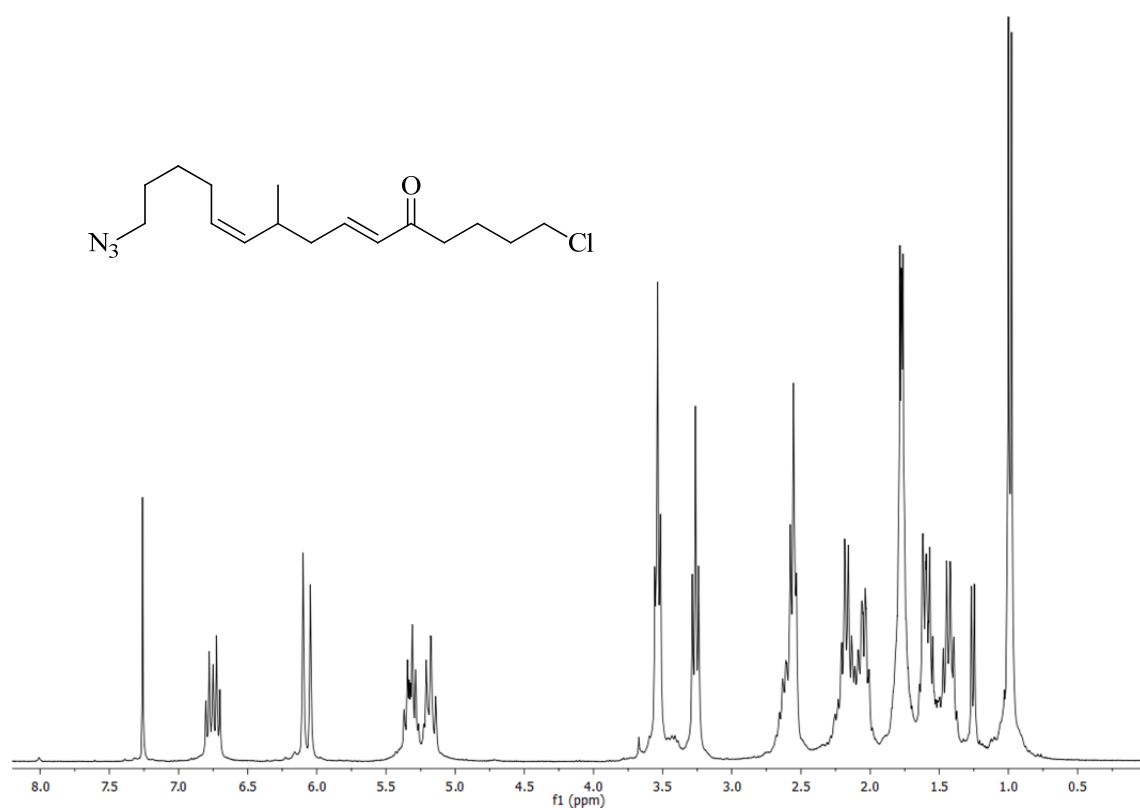
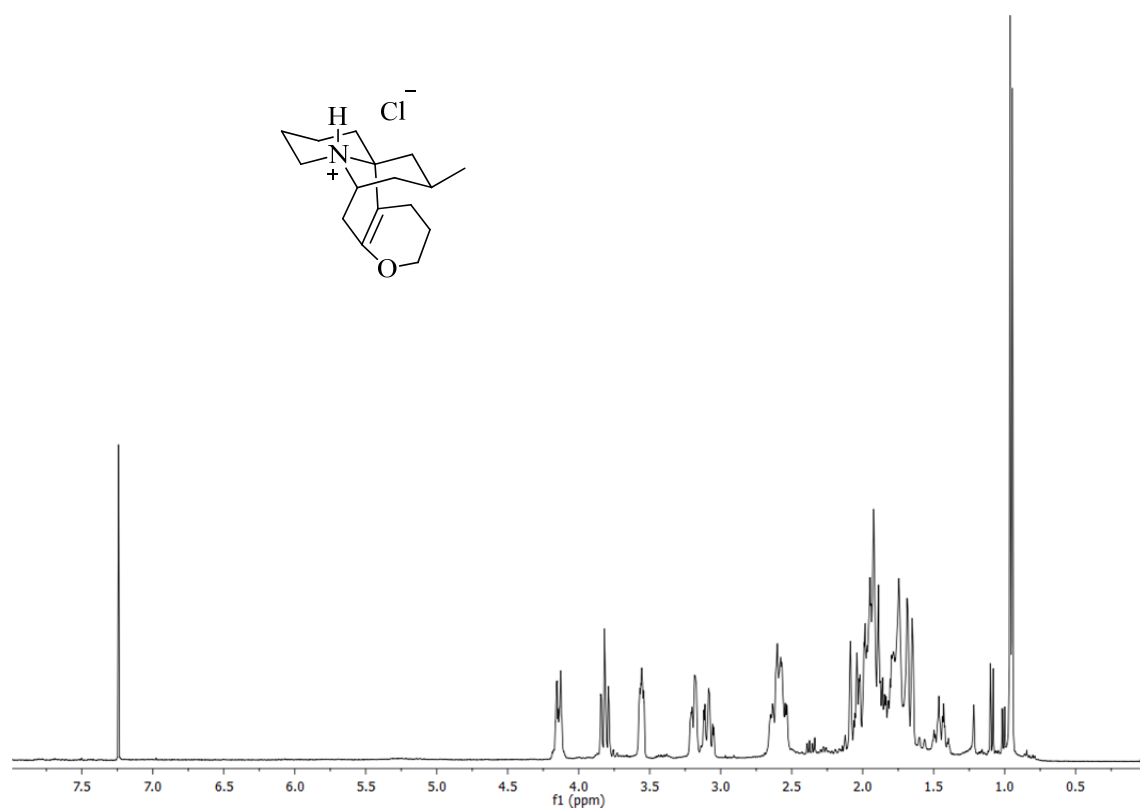
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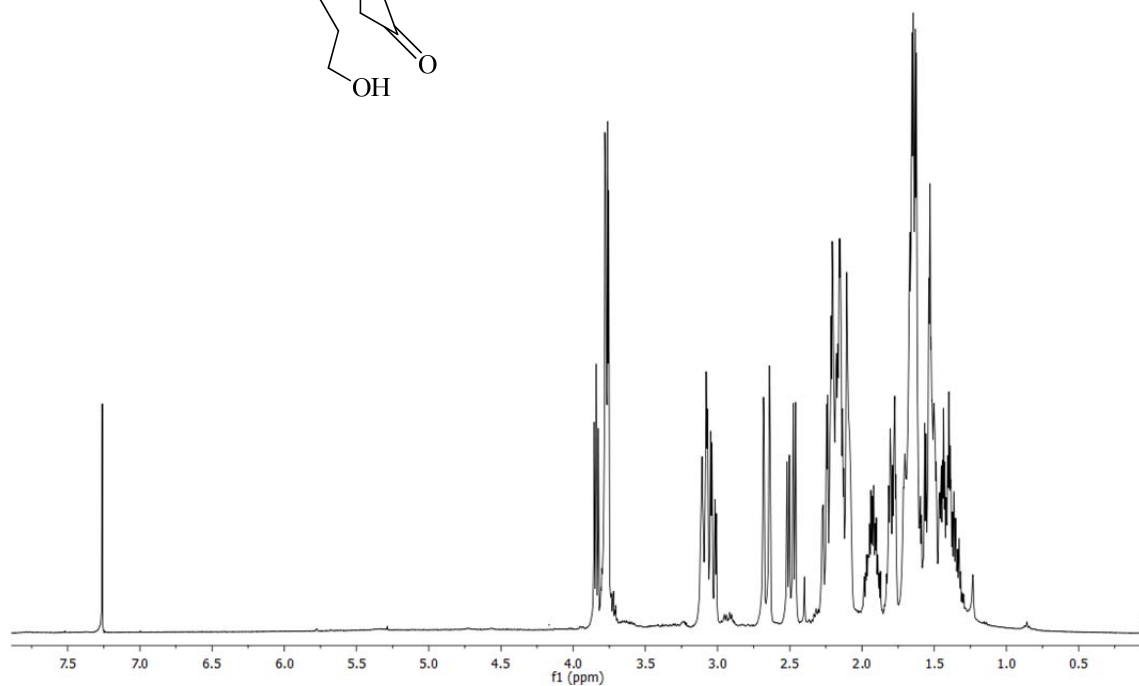
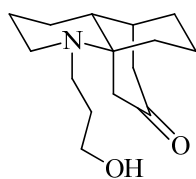
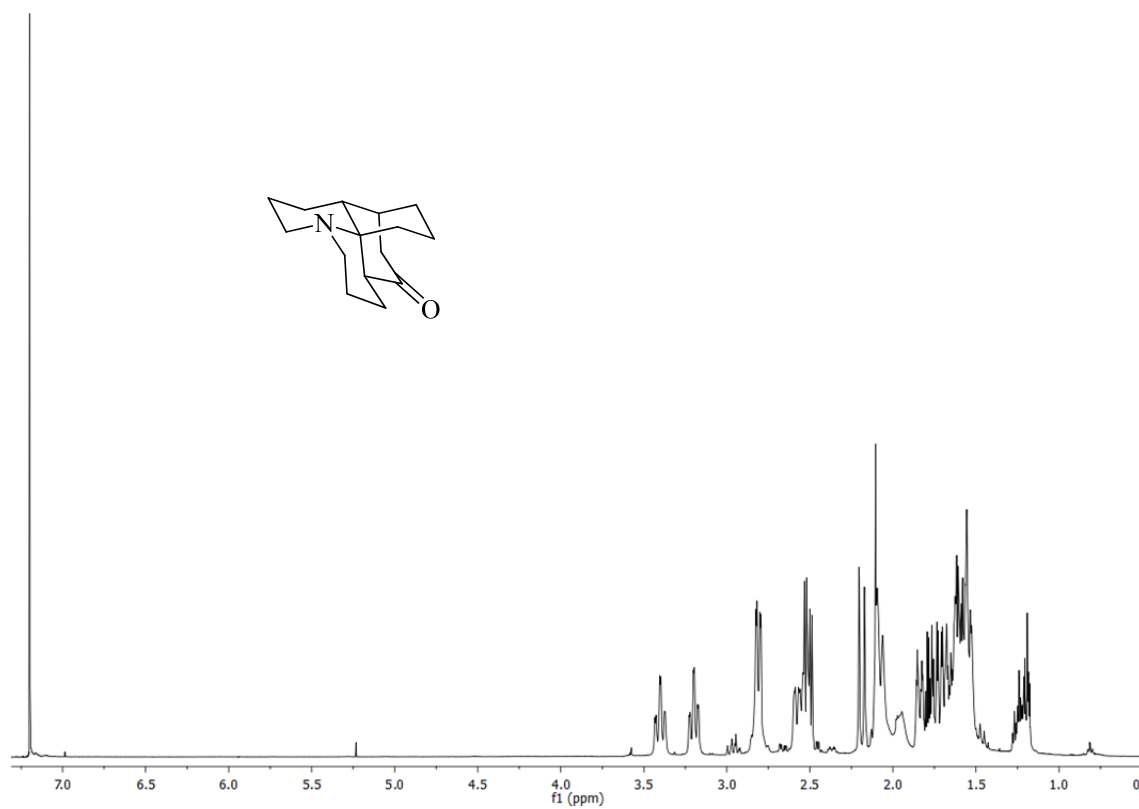
^1H -RMN del compuesto **105** ^1H -RMN del compuesto **109**

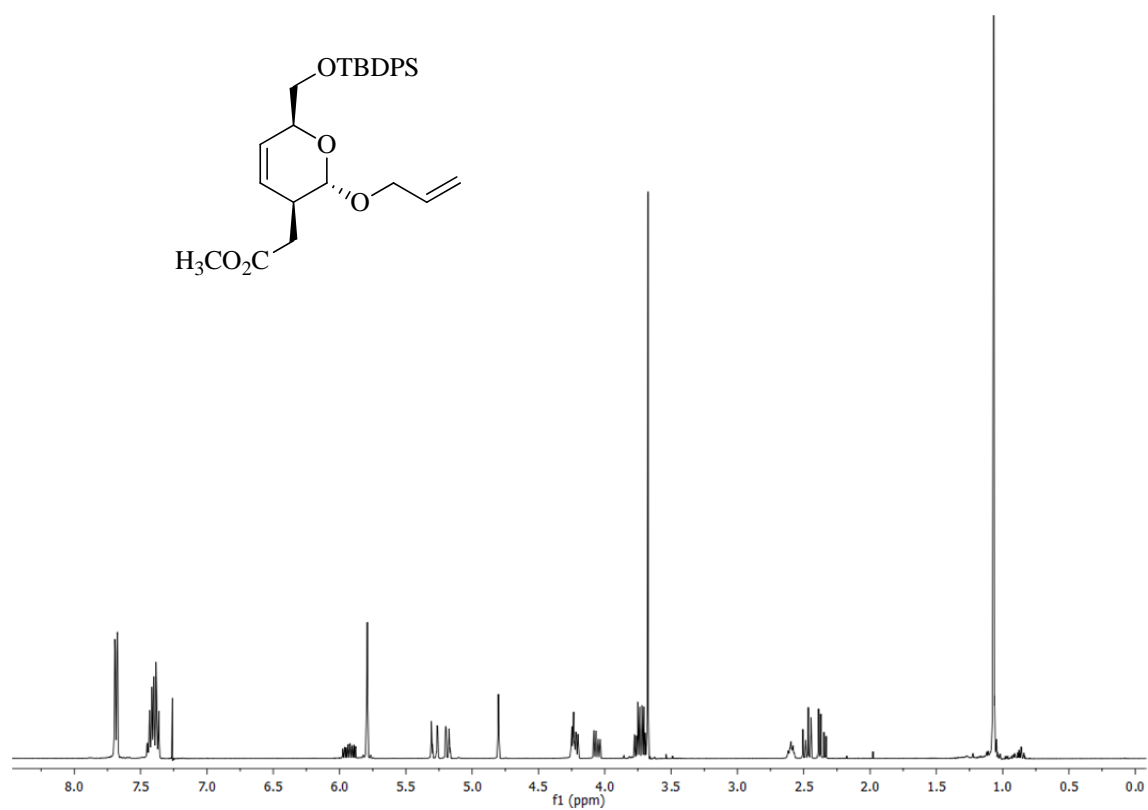
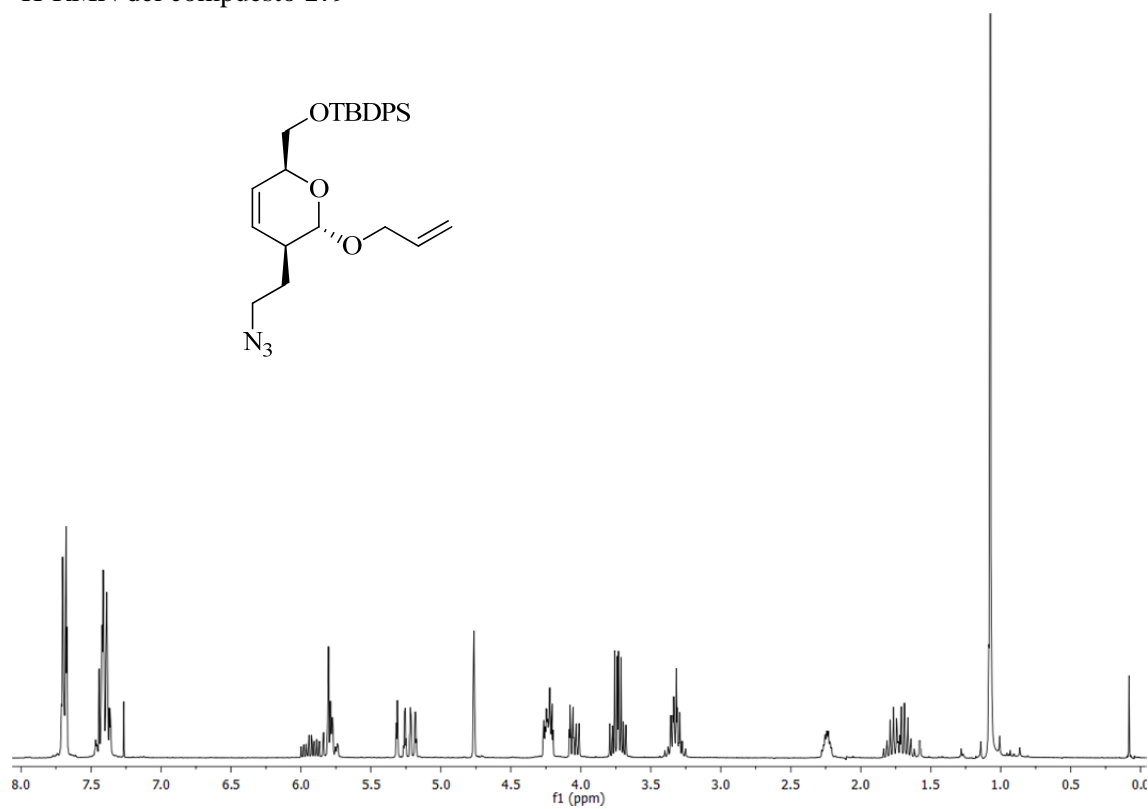
^1H -RMN del compuesto **115** ^1H -RMN del compuesto **117**

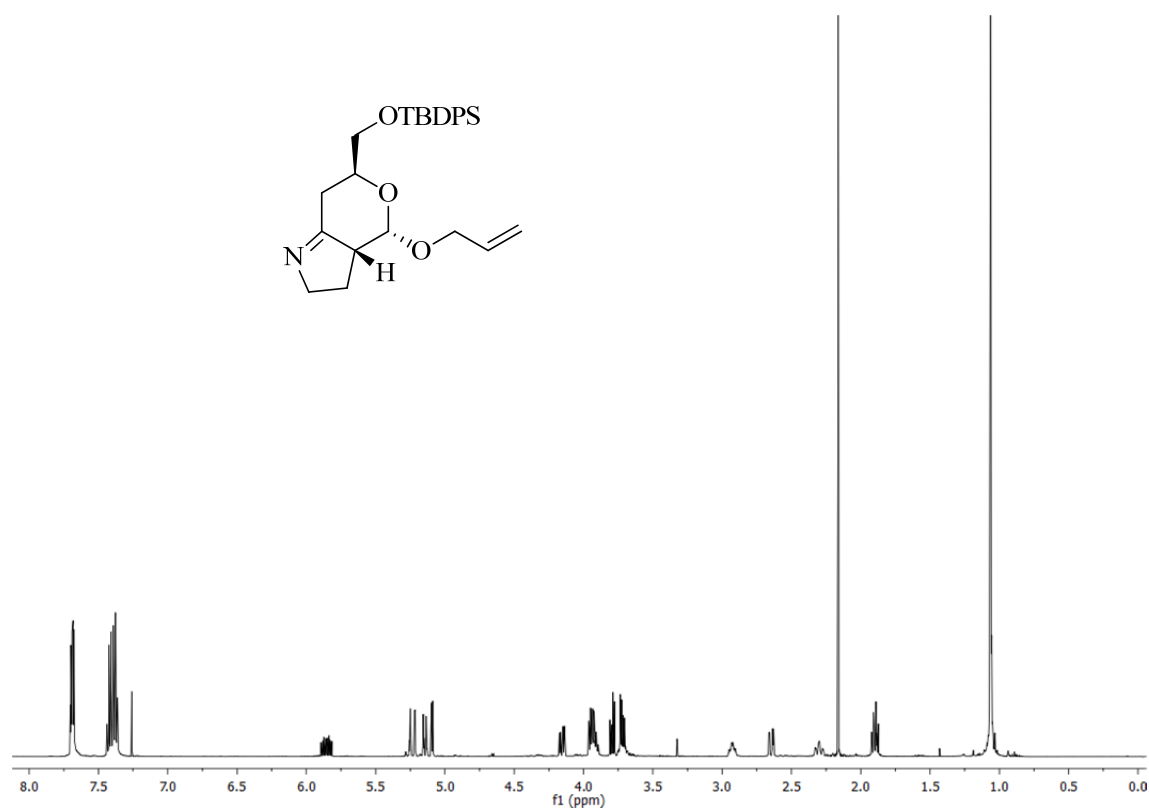
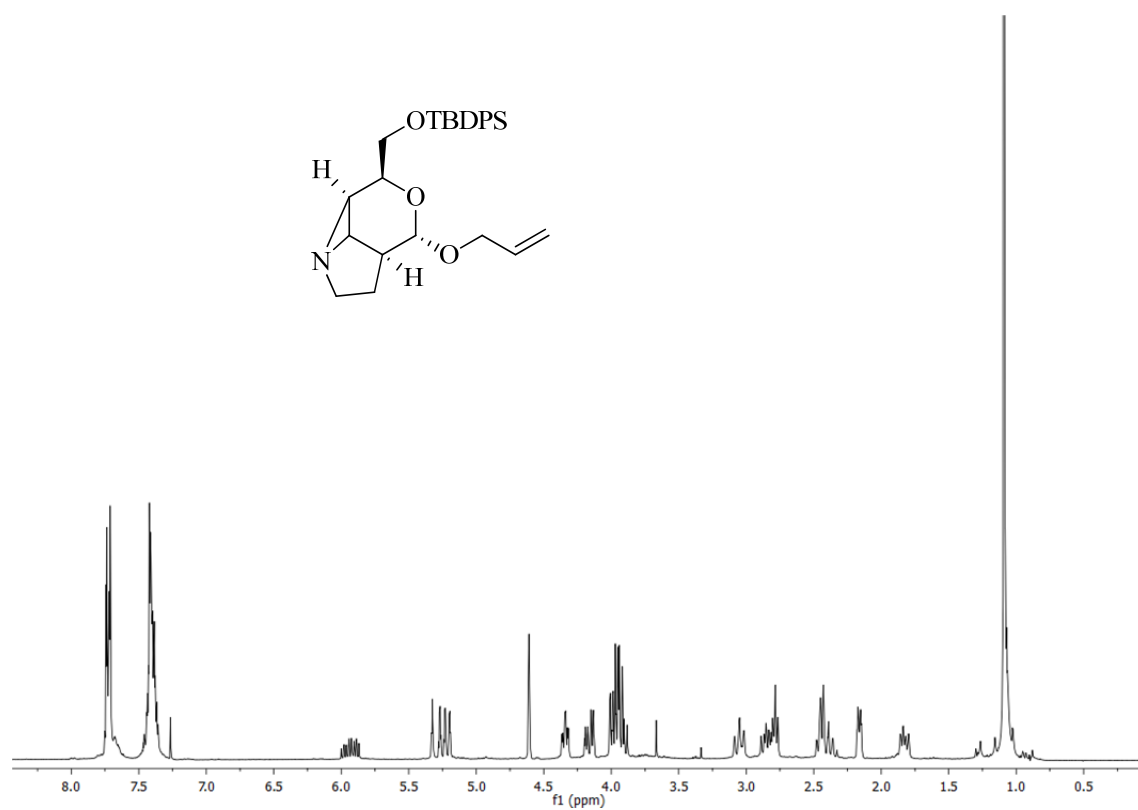
^1H -RMN del compuesto **121** ^1H -RMN del compuesto **130**

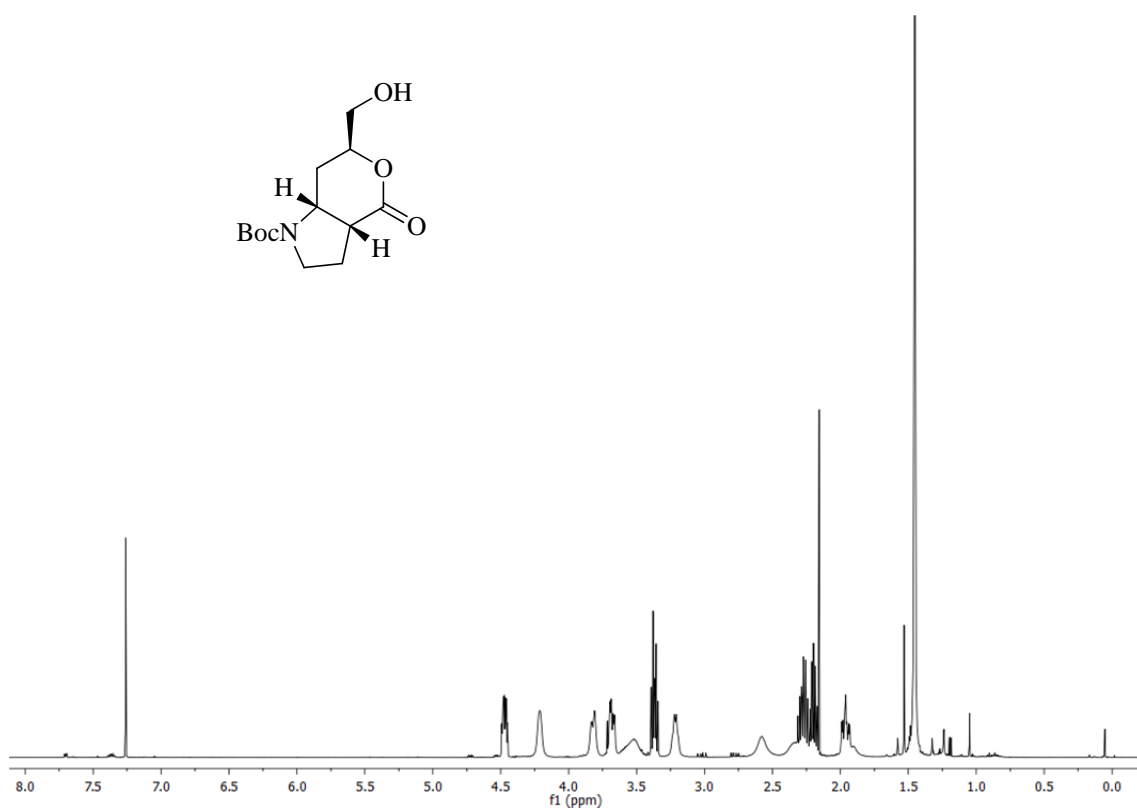
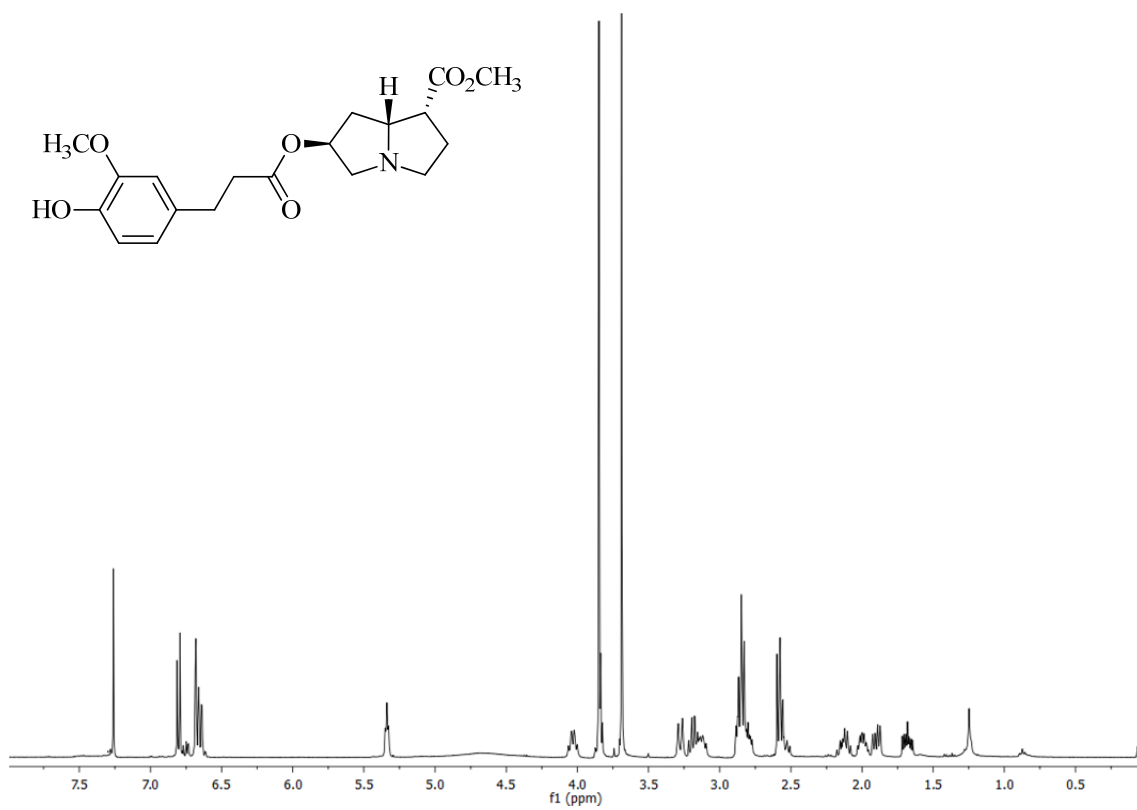
^1H -RMN del compuesto **143** ^1H -RMN del compuesto **144**

^1H -RMN del compuesto **149** ^1H -RMN del compuesto **154**

^1H -RMN del compuesto **168** ^1H -RMN del compuesto **170**

^1H -RMN del compuesto **176** ^1H -RMN del compuesto **179**

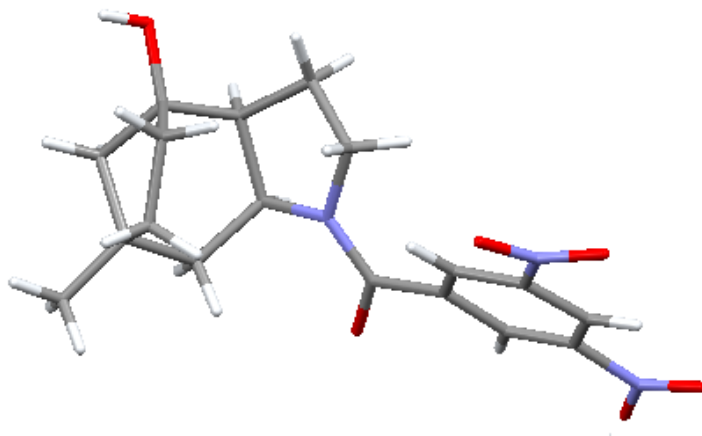
^1H -RMN del compuesto **180** ^1H -RMN del compuesto **181**

^1H -RMN del compuesto **188** ^1H -RMN del compuesto **194**

Anexo II

DIFRACCIÓN DE RAYOS X

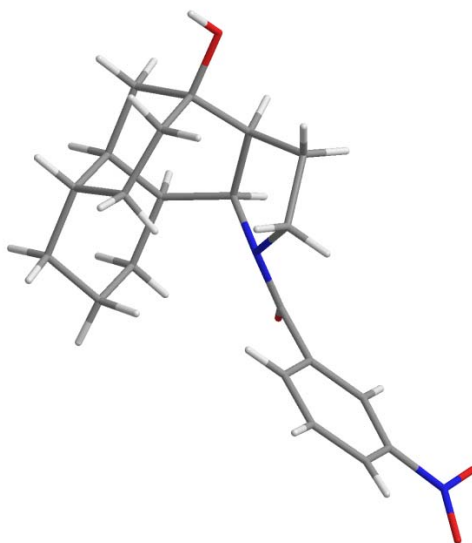
Datos de difracción de rayos-X para el compuesto **29**.



Empirical formula	C ₁₈ H ₂₁ N ₃ O ₆	
Formula weight	375.38	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.8402(16) Å	α = 89.383(7)°.
	b = 13.1113(19) Å	β = 68.313(7)°.
	c = 13.929(2) Å	γ = 71.556(7)°.
Volume	1732.4(4) Å ³	
Z	4	
Density (calculated)	1.439 Mg/m ³	
Absorption coefficient	0.109 mm ⁻¹	
F(000)	792	
Crystal size	0.28 x 0.25 x 0.20 mm ³	
Theta range for data collection	1.58 to 28.70°.	
Index ranges	-14 ≤ h ≤ 14, -17 ≤ k ≤ 17, -18 ≤ l ≤ 18	
Reflections collected	70239	
Independent reflections	8885 [R(int) = 0.0597]	
Completeness to theta = 28.70°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9784 and 0.9700	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	8885 / 0 / 497	
Goodness-of-fit on F ²	1.016	
Final R indices [I > 2σ(I)]	R1 = 0.0404, wR2 = 0.0955	

R indices (all data)	$R1 = 0.0652$, $wR2 = 0.1082$
Largest diff. peak and hole	0.412 and -0.275 e.Å^{-3}

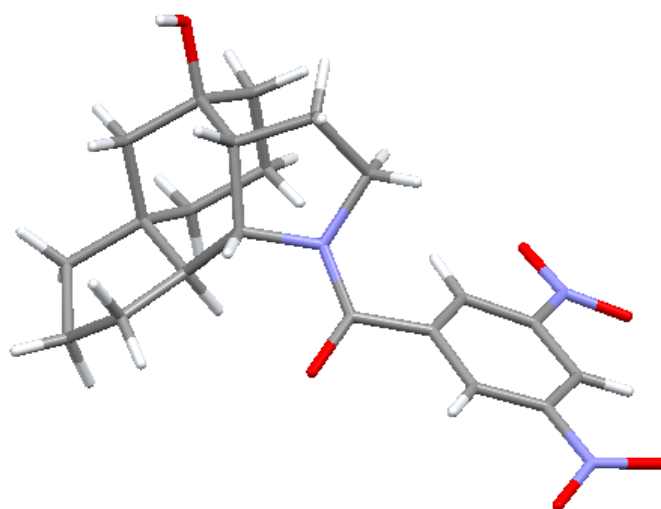
Datos de difracción de rayos-X para el compuesto **48**.



Empirical formula	C ₂₁ H ₂₆ N ₂ O ₄	
Formula weight	370.44	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	$a = 11.7373(2) \text{ Å}$	$\alpha = 90^\circ$.
	$b = 11.2429(2) \text{ Å}$	$\beta = 104.6380(10)^\circ$.
	$c = 13.9114(3) \text{ Å}$	$\gamma = 90^\circ$.
Volume	$1776.18(6) \text{ Å}^3$	
Z	4	
Density (calculated)	1.385 Mg/m^3	
Absorption coefficient	0.781 mm^{-1}	
F(000)	792	
Crystal size	$0.20 \times 0.18 \times 0.12 \text{ mm}^3$	

Theta range for data collection	5.13 to 69.31°.
Index ranges	-14≤h≤13, -12≤k≤13, -16≤l≤16
Reflections collected	12085
Independent reflections	3200 [R(int) = 0.0333]
Completeness to theta = 69.31°	96.2 %
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3200 / 0 / 348
Goodness-of-fit on F ²	1.040
Final R indices [I>2sigma(I)]	R1 = 0.0397, wR2 = 0.1021
R indices (all data)	R1 = 0.0418, wR2 = 0.1040
Largest diff. peak and hole	0.351 and -0.220 e.Å ⁻³

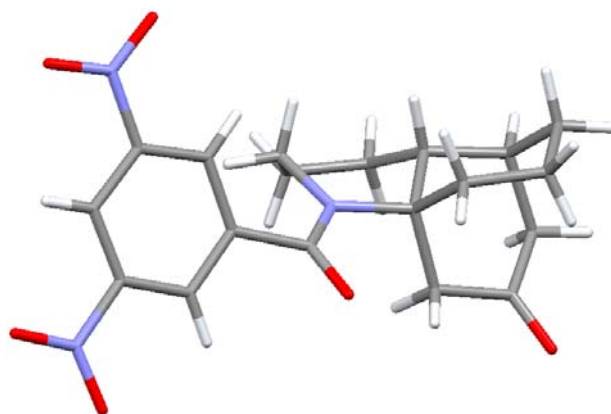
Datos de difracción de rayos-X para el compuesto **56**.



Empirical formula	C ₂₁ H ₂₅ N ₃ O ₆
Formula weight	415.44
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pna2(1)
Unit cell dimensions	a = 20.972(2) Å α = 90°.

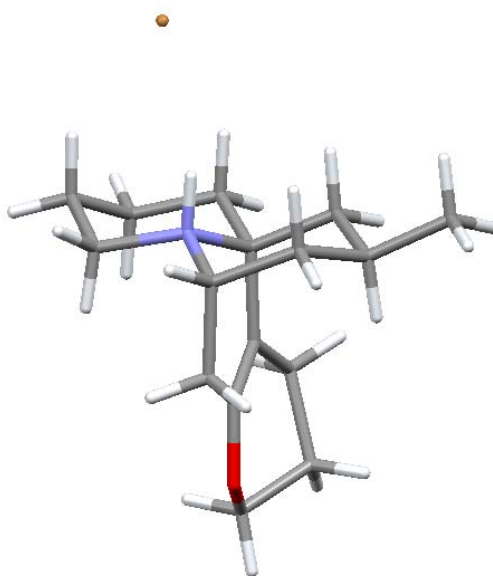
	$b = 6.8683(7) \text{ \AA}$	$\beta = 90^\circ$.
	$c = 13.1808(12) \text{ \AA}$	$\gamma = 90^\circ$.
Volume	$1898.6(3) \text{ \AA}^3$	
Z	4	
Density (calculated)	1.453 Mg/m^3	
Absorption coefficient	0.108 mm^{-1}	
F(000)	880	
Crystal size	$0.25 \times 0.20 \times 0.10 \text{ mm}^3$	
Theta range for data collection	$2.48 \text{ to } 27.48^\circ$.	
Index ranges	$-27 \leq h \leq 27, -8 \leq k \leq 8, -17 \leq l \leq 17$	
Reflections collected	29052	
Independent reflections	4344 [R(int) = 0.0538]	
Completeness to $\theta = 27.48^\circ$	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9893 and 0.9736	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4344 / 1 / 272	
Goodness-of-fit on F^2	1.042	
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0363, wR2 = 0.0835$	
R indices (all data)	$R1 = 0.0431, wR2 = 0.0867$	
Absolute structure parameter	0.0(8)	
Largest diff. peak and hole	$0.257 \text{ and } -0.189 \text{ e.\AA}^{-3}$	

Datos de difracción de rayos-X para el compuesto **144**.



Empirical formula	C ₁₉ H ₂₁ N ₃ O ₆	
Formula weight	387.39	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 6.7855(2) Å	α = 90°.
	b = 16.8925(4) Å	β = 99.5780(10)°.
	c = 15.8265(4) Å	γ = 90°.
Volume	1788.81(8) Å ³	
Z	4	
Density (calculated)	1.438 Mg/m ³	
Absorption coefficient	0.109 mm ⁻¹	
F(000)	816	
Crystal size	0.370 x 0.160 x 0.160 mm ³	
Theta range for data collection	1.78 to 25.35°.	
Index ranges	-8 ≤ h ≤ 8, -20 ≤ k ≤ 20, -19 ≤ l ≤ 19	
Reflections collected	32202	
Independent reflections	3264 [R(int) = 0.0379]	
Completeness to theta = 25.35°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.98 and 0.89	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3264 / 0 / 253	
Goodness-of-fit on F ²	1.026	
Final R indices [I > 2σ(I)]	R1 = 0.0588, wR2 = 0.1807	
R indices (all data)	R1 = 0.0746, wR2 = 0.2056	
Largest diff. peak and hole	0.792 and -0.255 e.Å ⁻³	

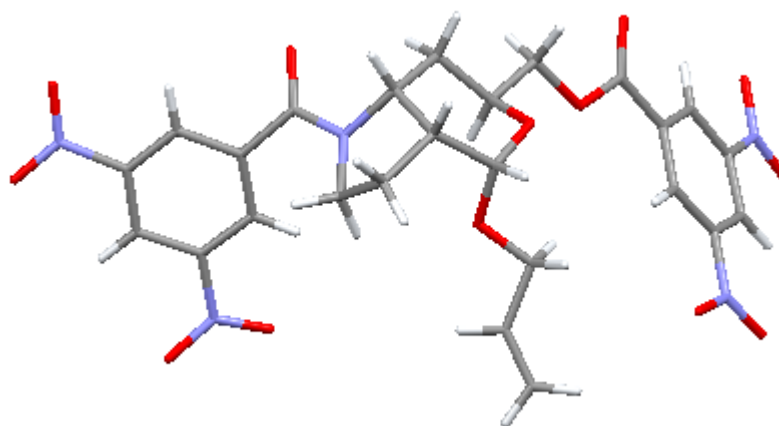
Datos de difracción de rayos-X para el compuesto **154**.



Empirical formula	C ₁₆ H ₂₆ Br N O	
Formula weight	328.29	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.6275(4) Å	α = 79.800(2)°.
	b = 9.4348(4) Å	β = 83.376(2)°.
	c = 10.9060(5) Å	γ = 67.892(2)°.
Volume	808.31(6) Å ³	
Z	2	
Density (calculated)	1.349 Mg/m ³	
Absorption coefficient	2.537 mm ⁻¹	
F(000)	344	
Crystal size	0.22 x 0.18 x 0.12 mm ³	
Theta range for data collection	1.90 to 28.38°.	
Index ranges	-11 ≤ h ≤ 11, -12 ≤ k ≤ 12, -14 ≤ l ≤ 14	
Reflections collected	23425	
Independent reflections	4026 [R(int) = 0.0348]	
Completeness to theta = 28.38°	99.2 %	
Absorption correction	None	
Max. and min. transmission	0.7506 and 0.6053	
Refinement method	Full-matrix least-squares on F ²	

Data / restraints / parameters	4026 / 0 / 174
Goodness-of-fit on F^2	1.000
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0600$, $wR2 = 0.2110$
R indices (all data)	$R1 = 0.0724$, $wR2 = 0.2303$
Extinction coefficient	0.078(12)
Largest diff. peak and hole	1.541 and -0.755 e.Å ⁻³

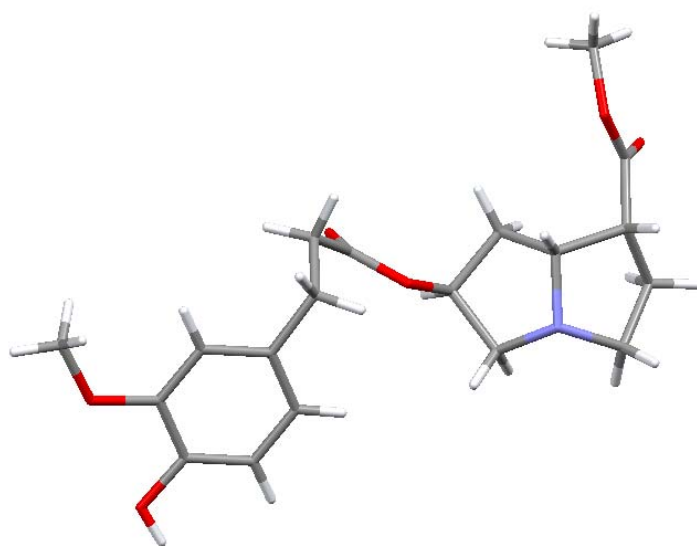
Datos de difracción de rayos-X para el compuesto **183**.



Empirical formula	C ₂₅ H ₂₃ N ₅ O ₁₃	
Formula weight	601.48	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	$a = 10.0736(4)$ Å	$\alpha = 90^\circ$.
	$b = 11.6400(3)$ Å	$\beta = 90^\circ$.
	$c = 22.6872(8)$ Å	$\gamma = 90^\circ$.
Volume	2660.23(16) Å ³	
Z	4	
Density (calculated)	1.502 Mg/m ³	
Absorption coefficient	0.124 mm ⁻¹	
F(000)	1248	

Crystal size	0.20 x 0.18 x 0.12 mm ³
Theta range for data collection	1.80 to 25.31°.
Index ranges	-12<=h<=12, -13<=k<=13, -27<=l<=27
Reflections collected	28767
Independent reflections	4814 [R(int) = 0.0430]
Completeness to theta = 25.31°	99.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9853 and 0.9757
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	4814 / 1 / 388
Goodness-of-fit on F ²	1.103
Final R indices [I>2sigma(I)]	R1 = 0.0449, wR2 = 0.1123
R indices (all data)	R1 = 0.0723, wR2 = 0.1338
Absolute structure parameter	1.5(13)
Largest diff. peak and hole	0.321 and -0.360 e.Å ⁻³

Datos de difracción de rayos-X para la **Amforoginina C**.



Empirical formula	C ₁₉ H ₂₅ N O ₆
Formula weight	363.40
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic

Space group	P2(1)	
Unit cell dimensions	a = 11.6549(4) Å	$\alpha = 90^\circ$.
	b = 5.5308(3) Å	$\beta = 92.138(2)^\circ$.
	c = 13.9417(6) Å	$\gamma = 90^\circ$.
Volume	898.07(7) Å ³	
Z	2	
Density (calculated)	1.344 Mg/m ³	
Absorption coefficient	0.100 mm ⁻¹	
F(000)	388	
Crystal size	0.10 x 0.12 x 0.25 mm ³	
Theta range for data collection	1.46 to 28.38°.	
Index ranges	-15 ≤ h ≤ 11, -7 ≤ k ≤ 7, -18 ≤ l ≤ 18	
Reflections collected	11336	
Independent reflections	2454 [R(int) = 0.0544]	
Completeness to theta = 28.38°	99.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2454 / 1 / 238	
Goodness-of-fit on F ²	1.085	
Final R indices [I > 2σ(I)]	R1 = 0.0464, wR2 = 0.1069	
R indices (all data)	R1 = 0.0906, wR2 = 0.1594	
Absolute structure parameter	-1(2)	
Largest diff. peak and hole	0.210 and -0.202 e.Å ⁻³	

Anexo III

PUBLICACIONES DERIVADAS DE ESTE TRABAJO

Intramolecular Azide-Alkene 1,3-Dipolar Cycloaddition/Enamine Addition(s) Cascade Reaction: Synthesis of Nitrogen-Containing Heterocycles

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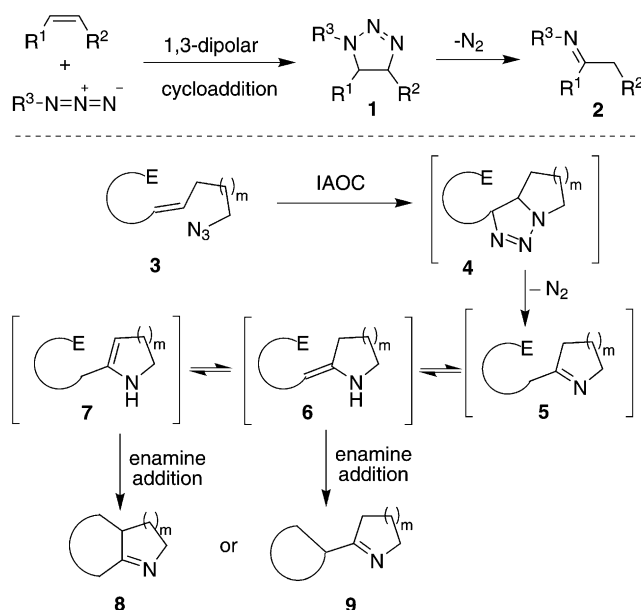
Abstract: A cascade intramolecular azide-alkene 1,3-dipolar cycloaddition/1,2 enamine and/or 1,4 enamine addition reaction sequence has been developed, and provides access to a variety of nitrogen containing heterocycles from readily available ω -azido alkenes.

Keywords: azides; conjugated addition; cycloaddition; enamines; ketimines

The development of new cascade processes is a topic of major interest in organic synthesis.^[1] These transformations are generally accompanied by a rapid increase in structural complexity. Furthermore, concepts such as “atom economy”,^[2] “steps economy”^[3] or “redox economy”^[4] are inherent to them. In particular, cascade reactions involving the formation of C–C bonds in a stereoselective way are of special importance due to the fundamental role of this transformation in the design of almost any synthetic plan.^[5]

In connection with our interest in the stereoselective synthesis of nitrogen-containing heterocyclic compounds,^[6] herein we report our preliminary findings on an efficient cascade reaction that is well-suited for the preparation of complex and diverse pyrrolidine- and piperidine-containing polycyclic heterocycles.^[7]

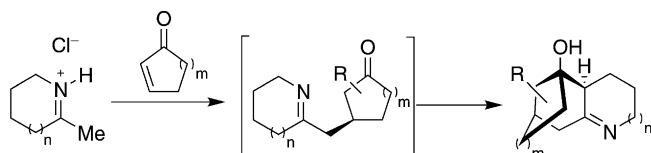
Under thermal conditions, azides react with olefins through a 1,3-dipolar cycloaddition reaction to form 1,2,3- Δ^2 -triazolines (**1**)^[8] that, unlike their aromatic analogues, 1,2,3-triazoles, are in general not isolable and evolve after nitrogen loss to the corresponding imines (**2**) (Scheme 1). In particular, the intramolecular azide-olefin cycloaddition reaction (IAOC), has found broad application in the synthesis of complex molecules.^[9] We envisioned that cyclic ketimines **5** generated from the IAOC reaction of readily avail-



Scheme 1. IAOC/enamine addition cascade reaction.

able ω -azidoalkenes **3** (Scheme 1), after decomposition of the resulting triazolines (**4**), could tautomerize to the corresponding exocyclic (**6**) and endocyclic (**7**) enamines and react with a conveniently located electrophilic functionality to afford imines **8** or **9** in one single synthetic operation. Thus, the success of this approach relies on the intrinsic reactivity of the imine functional group, and the correct position of the electrophile group with respect to the enamine location.

Movassaghi and Chen recently reported an intermolecular formal [3+3] cycloaddition of cyclic enamines and cyclic enones that provides tricyclic imino alcohols in a stereoselective way (Scheme 2).^[10] This methodology was successfully applied to the elegant synthesis of galbulimima alkaloids GB-13^[11] and himandrine.^[12] In order to test our working hypotheses, we chose some members of that kind of tricyclic imino alcohols as model targets.

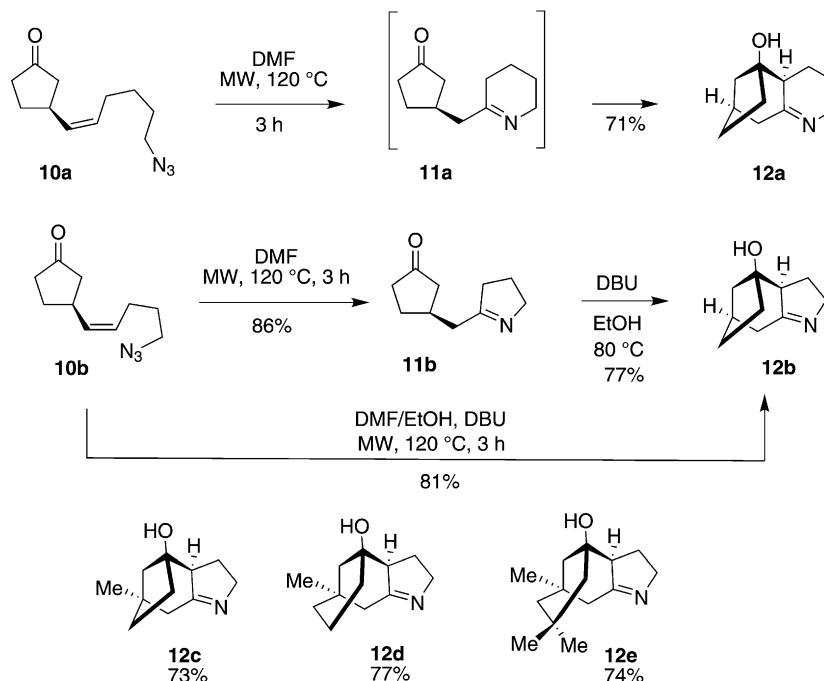


Scheme 2. Movassaghi's intermolecular [3+3] cycloaddition.

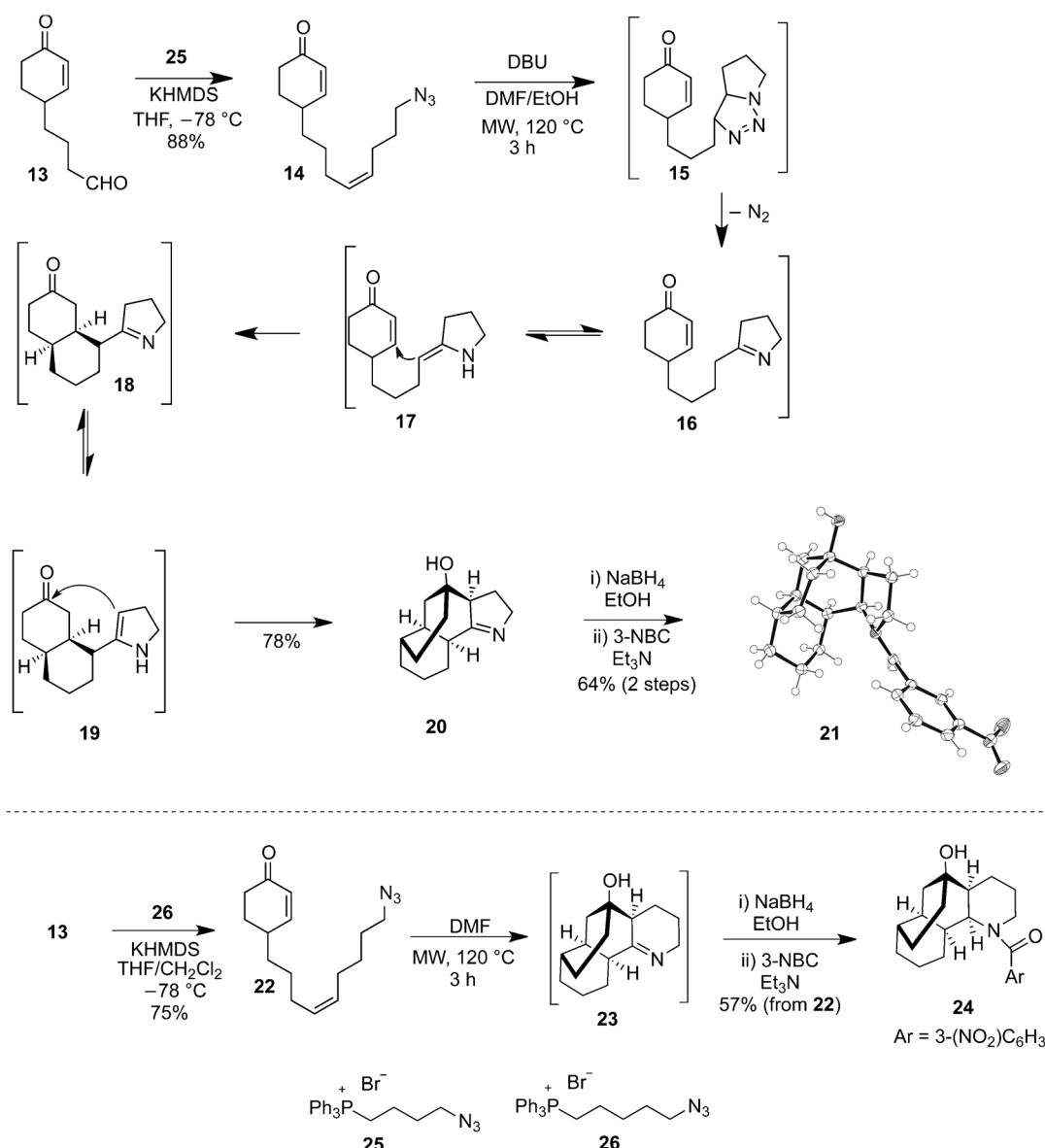
Initial studies were performed with ω -azido alkenes **10a** and **b** (Scheme 3), synthesized in three steps from cyclopenten-2-one.^[13] After screening different reaction conditions it was found that the employment of anhydrous dimethylformamide (DMF) as solvent was critical for optimal results. We were pleased to find that heating a solution of ω -azidoalkene **10a** in DMF in a sealed tube at 120 °C for 14 h afforded tricyclic amino alcohol **12a** as a single diastereomer in 64% yield. Gratifyingly, when the reaction was performed under similar conditions but under microwave irradiation, compound **12a** was obtained in 71% yield in only 3 h. On the other hand, when ω -azidoalkene **10b** was subjected to the same protocol, only cyclic imino ketone **11b** was isolated in 86% yield. Treatment of **11b** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing ethanol, as previously reported,^[10] afforded imino alcohol **12b** in 77% yield as a single diastereomer. Interestingly, we observed that just treating **10b** with DBU in a DMF/ethanol mixture under microwave irradiation provided compound **12b** in a single synthetic operation in an excellent 81% yield, avoiding the necessity of isolating the intermediate imino ketone **11b** (Scheme 3).

Applying the optimized conditions for this cascade reaction, we also prepared imino alcohols **12c–e**, starting from the correspondent ω -azidoalkenes.^[13] Formation of the corresponding aziridines resulting of decomposition of the unstable triazoline intermediates was not detected in any case. While related with the methodology described by Movassaghi, our approach is fundamentally different in the way that the enamine group is introduced in the molecule and, since it is not only limited to the use of cyclic enones (*vide infra*), it allows an access to compounds of wide structural diversity.

We next turned our attention to the application of this methodology to more complex substrates. Due to the presence of two non-equivalent nucleophilic positions (Ca and Ca') in the transient cyclic ketoimines generated after triazoline decomposition, we postulated that sequential 1,4-addition/1,2-addition of these ketoimines to a conveniently located enone functionality would afford the corresponding tetracyclic imino alcohols in a single synthetic operation. As shown in Scheme 4, Wittig reaction of readily available aldehyde **13**^[13] with known azidophosphonium salt **25**^[14] employing KHMDS as base, gave (*Z*)- ω -azidoalkene **14** in good yield. When compound **14** was subjected to our optimized conditions described above, tetracyclic imino alcohol **20** was obtained as a single diastereomer in 78% yield. Hypothetically, formation of **20** probably proceeds by an initial IAOC followed by triazoline decomposition that would afford the cyclic imine **16**. Tautomerization of **16** to the corresponding exocyclic enamine **17** and subsequent conjugate addi-



Scheme 3. One-pot synthesis of compounds **12a–e**.



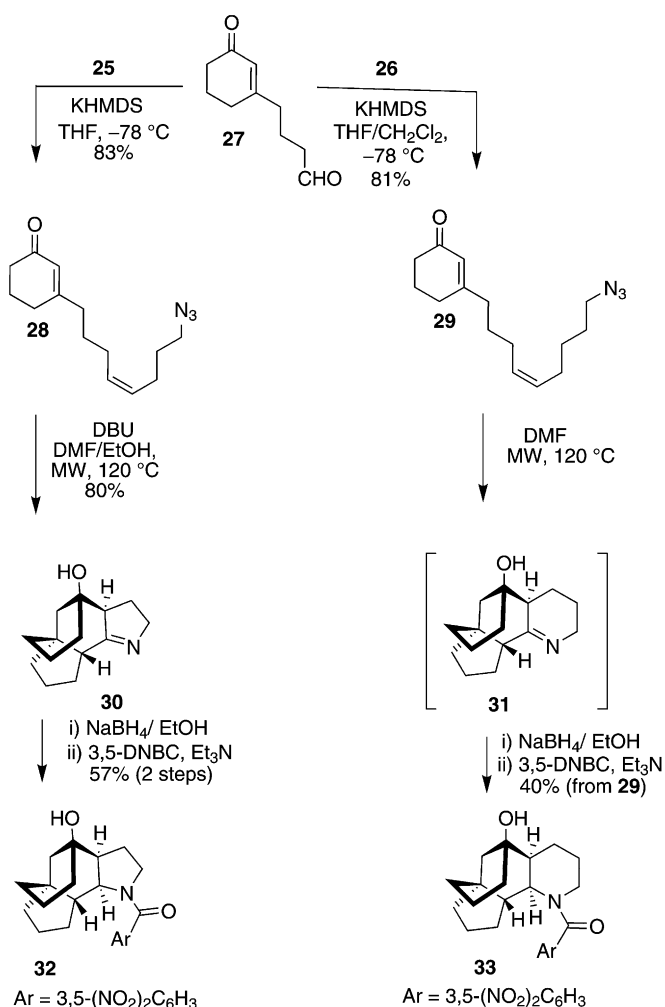
Scheme 4. Synthesis of tetracyclic imino alcohols **20** and **23**.

tion to the enone functionality would afford imino ketone **18**, which might undergo a second tautomerization to the endocyclic enamine **19** and final addition to the carbonyl group to give **20**. Four stereogenic centers and three new rings are formed during this 1,3 dipolar cycloaddition/1,4 addition/1,2 addition cascade process. Finally, **20** was converted into 3-nitrobenzoyl derivative **21** and the relative stereochemistry of the six contiguous stereocenters present in this molecule was confirmed by X-ray diffraction analysis.^[15] Formally, this transformation corresponds to the intramolecular version of the Movassaghi formal [3+3] cycloaddition reaction.

Employing azidophosphonium salt **26**, (*Z*)- ω -azidoalkene **22** was prepared from aldehyde **13** in a similar fashion. In this case, we observed that the pres-

ence of dichloromethane as cosolvent (THF/ CH_2Cl_2 , 9:1) was critical for optimal results in the Wittig reaction. When compound **22** was subjected to the cyclization conditions, the stereoselective formation of tetracyclic imino alcohol **23** was observed. Due to the low stability of compound **23** towards air oxidation during isolation,^[16] it was converted into the 3-nitrobenzoyl derivative **24** for ease of isolation and characterization (Scheme 4).

We also tested this IAOC/double enamine addition process in compounds **28** and **29** (Scheme 5). Since **28** and **29** are 3-substituted enones, a stereogenic quaternary carbon center could be built after enamine conjugate addition. Aldehyde **27** (prepared in two steps from commercially available 3-ethoxy-2-cyclohexenone)^[13] was converted into ω -azidoalkenes **28** and **29**



Scheme 5. Synthesis of tetracyclic imino alcohols **30** and **31**.

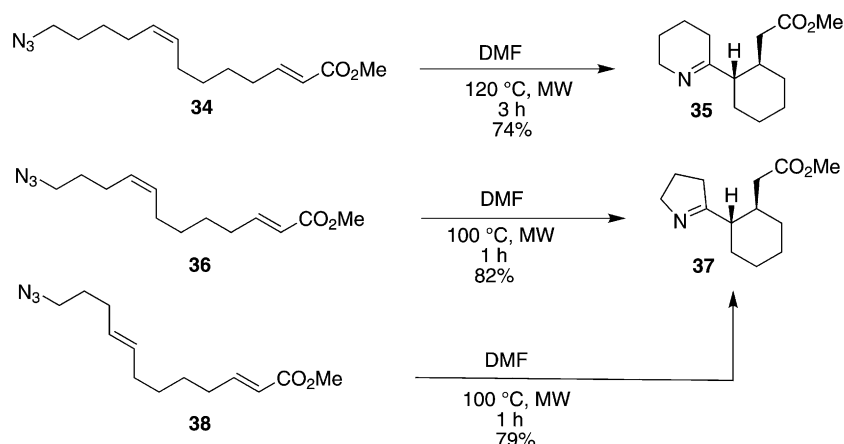
using a Wittig reaction. Subsequent heating of these compounds under optimized conditions afforded tetracyclic imino alcohols **30** and **31** respectively, which were separately converted into amido alcohols **32** and

33. The relative stereochemistry of imino alcohol **30** was confirmed by X-ray crystallographic analysis of the corresponding amido alcohol **32**.^[15]

There are interesting aspects to this cascade process: as in compounds **20** and **23**, (Scheme 4) four stereogenic centers (two of them quaternary) and three new cycles are created in a single synthetic operation, but while in **20** and **23** the final stereochemistry is dictated by the configuration of the stereogenic center already present in the ω -azidoalkenes **14** and **22**, in the case of imino alcohols **30** and **31** the cyclization precursors (**28** and **29**) are achiral. This fact implies the possibility of applying asymmetric synthesis methodologies based on enone activation in order to access to enantiomerically pure derivatives.^[17]

Finally, the possibility of carrying out the IAOC/enamine addition sequence with acyclic substrates was examined (Scheme 6). When a DMF solution of linear ω -azidoalkene **34**^[13] was heated at 120 °C for three hours under microwave irradiation, the bicyclic imino ester **35** was obtained in 74% yield as a single diastereomer. Imino ester **37** was prepared from ω -azidoalkene **36** in a similar way in 82% yield, but in this case lower temperature (100 °C) and shorter reaction time (1 h) were required. In order to examine the influence of the alkene geometry on the reaction outcome, compound **38** was prepared and subjected to our cyclization conditions. Treating a solution of (*E,E*)-azidoalkene **38** in DMF under the same conditions employed for its isomer **36**, also furnished bicyclic imino ester **37** in a similar yield. This result indicates that neither the efficiency nor the stereochemical outcome of the process is affected by the geometry of the employed starting ω -azidoalkene.

In summary, an efficient stereoselective intramolecular azide-olefin cycloaddition/enamine addition(s) reaction cascade of ω -azidoalkenes for the preparation of diverse complex polycyclic nitrogen-containing structures has been developed. Further developments of this methodology, including mechanistic insights



Scheme 6. IAOC/enamine addition cascade reaction with linear substrates.

and an enantioselective version as well as its application to the total synthesis of different alkaloids are currently in progress and will be reported in due course.

Experimental Section

Caution: All organic azides should be treated as potential explosion hazards.

rac-(1*S*,4*S*,8*S*,13*S*,15*R*)-10-Azatetracyclo[6.5.2.0^{4,15}.0^{9,13}]pentadec-9-en-1-ol (**20**)

DBU (0.18 mL, 1.20 mmol) was added to a solution of compound **14** (100 mg, 0.40 mmol) in DMF/ethanol (10 mL, 4:1). The mixture was heated in a microwave reactor at 120°C for 3 h. The dark brown solution was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, gradient from DCM to 97:3 DCM:MeOH) to afford the desired imino alcohol **19** as a pale yellow viscous oil; yield: 68 mg (78%). ¹H NMR (400 MHz, CDCl₃): δ = 3.99 (m, 1H), 3.57 (m, 1H), 2.73 (app t, *J* = 9.6 Hz, 1H), 2.41 (m, 2H), 2.16 (m, 1H), 2.08 (m, 1H), 1.94 (m, 1H), 1.82 (m, 2H), 1.76–1.71 (m, 2H), 1.52–1.42 (m, 4H), 1.30 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ = 179.9, 71.2, 59.1, 58.7, 44.8, 38.7, 38.5, 35.0, 34.7, 30.7, 26.5, 24.3, 23.2, 15.7; FT-IR (neat): ν_{max} = 3330, 2950, 2860, 1649, 1460 cm⁻¹; HR-MS-ESI: *m/z* = 220.1695, calcd. for C₁₄H₂₂NO [M+H]⁺: 220.1696.

rac-(3-Nitrophenyl){(1*S*,4*S*,8*S*,9*S*,13*S*,15*R*)-1-hydroxy-10-azatetracyclo[6.5.2.0^{4,15}.0^{9,13}]pentadecan-10-yl}-methanone (**21**)

Sodium borohydride (13 mg, 0.36 mmol) was added to a solution of compound **20** (40 mg, 0.18 mmol) in absolute ethanol (5 mL) at 0°C. After 45 min the reaction mixture was quenched with saturated NH₄Cl solution and concentrated under reduced pressure. The residue was diluted with aqueous NaOH solution (1 N, 5 mL) and thoroughly extracted with CH₂Cl₂ (3 × 30 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated under vacuum. The crude material was dissolved in CH₂Cl₂ (10 mL) and cooled to 0°C. Et₃N (50 μL, 0.36 mmol) and 3-nitrobenzoyl chloride (50 mg, 0.27 mmol) were sequentially added. After stirring at room temperature for 8 h the reaction mixture was quenched with saturated NH₄Cl solution and the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO₄, filtered and concentrated under vacuum. The crude solid was purified by chromatography (silica gel, gradient from 8:2 to 3:7 hexanes:EtOAc) to afford compound **21** as a white solid; yield: 43 mg (64%); mp 187–189°C. The relative stereochemistry of **21** was confirmed by X-ray crystallographic analysis (see the Supporting Information). ¹H NMR (400 MHz, CDCl₃): δ = 8.46 (m, 1H), 8.31 (m, 1H), 7.95 (m, 1H), 7.62 (m, 1H), 4.86 (t, *J* = 8.6 Hz, 1H), 3.63 (m, 1H), 3.44 (m, 1H), 2.55 (m, 1H), 2.48 (t, *J* = 8.4 Hz, 1H), 2.38 (m, 1H), 2.10 (dd, *J* = 13.7, 6.1 Hz, 1H), 1.97 (m, 1H), 1.91 (m, 1H), 1.87 (m, 1H), 1.76 (m, 1H), 1.74 (m,

1H), 1.64 (m, 2H), 1.58–1.51 (m, 5H), 1.36 (m, 1H), 1.24 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 172.9, 148.4, 139.2, 134.4, 129.8, 125.7, 123.6, 70.4, 59.9, 54.3, 49.9, 45.3, 39.7, 37.1, 35.4, 33.9, 30.8, 28.4, 27.0, 25.3, 18.1; FT-IR (neat): ν_{max} = 3435, 2950, 1625, 1533, 1350 cm⁻¹; HR-MS-ESI: *m/z* = 371.1964, calcd. for C₂₁H₂₇N₂O₄ [M+H]⁺: 371.1968.

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First Total Synthesis of the Pyrrolizidine Alkaloid Amphorogynine C through Intramolecular Azide–Olefin Cycloaddition

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Keywords: Total synthesis / Alkaloids / Cycloaddition / Natural products / Azides

The first total synthesis of the natural alkaloid amphorogynine C is reported (2.9% overall yield in 20 steps). The key steps include a Claisen–Johnson rearrangement and an intramolecular azide–olefin cycloaddition, followed by a reduction of the resulting imine. The construction of the pyrrol-

izidine skeleton was achieved by an alkoxide-mediated lactone ring opening and subsequent cyclization of a conveniently functionalized bicyclic amine. Finally, the proposed structure of amphorogynine C was confirmed by single-crystal X-ray diffraction analysis.

Introduction

Because of their diverse structures and biological activities, pyrrolizidine alkaloids have attracted considerable synthetic interest during the previous decades.^[1] In 1998, four new pyrrolizidine alkaloids were isolated by Païs and co-workers from the New Caledonian plant *Amphorogynine spicata*.^[2] This class of compounds, named amphorogynines A, B, C, and D (**1–4**, Figure 1) are characterized by a double substitution pattern at the C-1 and C-6 positions of the bicyclic pyrrolizidine core. Prior to this work, two syntheses of amphorogynine A (**1**)^[3,4a] and one total synthesis of amphorogynine D (**4**)^[4b] were described. Herein, we report the first synthesis of amphorogynine C (**3**).

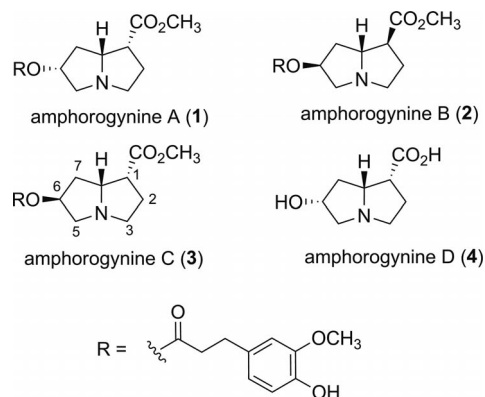


Figure 1. Chemical structures of amphorogynines A–D.

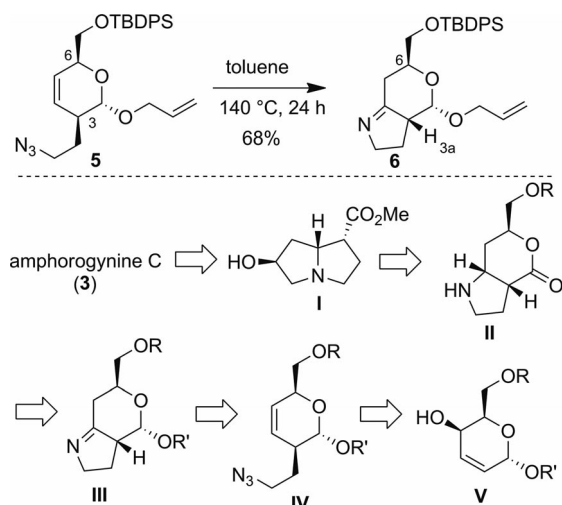
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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ejoc.201200384>.

Results and Discussion

In connection with our ongoing interest in the application of 1,3-dipolar azide–olefin cycloadditions to the syntheses of nitrogen-containing heterocycles and natural alkaloids,^[5] we prepared azidoalkene **5**. When this compound was heated at 140 °C in toluene (sealed tube), the corresponding imine **6** was formed, with total epimerization occurring at the C-3a position [Scheme 1 (top)]. A close inspection of the structure of compound **6** revealed that two of the stereogenic centers already present in this molecule, C-3a and C-6, have the same configuration as C-1 and C-6 of amphorogynine C (Figure 1). In addition, imine **6** already contains all of the carbon and nitrogen atoms (with the exception of the methoxy group of the carboxylate functionality) present in the bicyclic core of **3**. With these considerations in mind, the preparation of amphorogynine C was approached according to the retrosynthetic correlation summarized in Scheme 1 (bottom). The preparation of the 1-azabicyclo[3.3.0]octane **I** could be achieved by opening the lactone and subsequent cyclization of a conveniently functionalized derivative of bicyclic amine **II**. Intermediate **II** would result from a stereoselective reduction of the imine group, which would allow for the construction of the third stereogenic center present in amphorogynine C and subsequent oxidation of the anomeric position of **III**. This key intermediate might be secured by an intramolecular 1,3-dipolar azide–olefin cycloaddition of azidoalkene **IV**. This derivative of 3,6-dihydro-2H-pyran should be obtainable from allylic alcohol **V** by employing a Claisen–Johnson rearrangement as the key step.

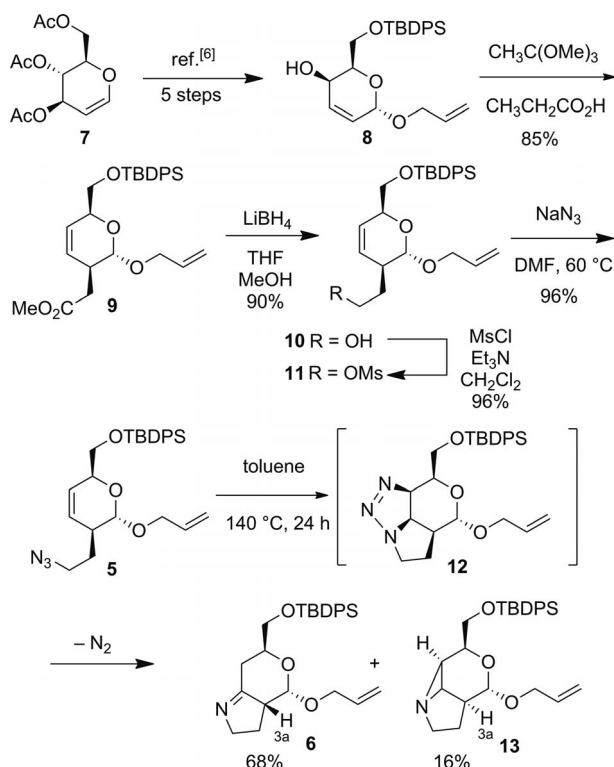
The synthesis of the key imine **6** is outlined in Scheme 2. The requisite starting material, allylic alcohol **8** was prepared on a multigram scale in five steps from commercially available 3,4,6-tri-O-acetyl-D-glucal (**7**) according to a method previously reported by our group.^[6] The Claisen–Johnson rearrangement was accomplished by heating to re-



Scheme 1. Key transformation of azide **5** into imine **6** (top), and retrosynthesis of amphorogynine C (**3**) (bottom).

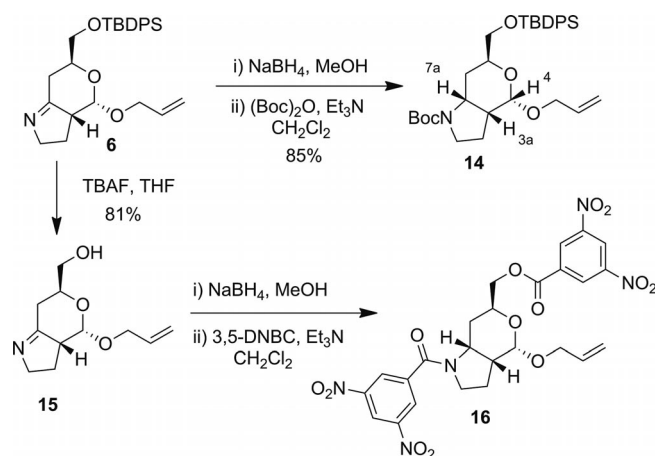
flux compound **8** in trimethyl orthoacetate in the presence of propanoic acid. This gave the corresponding γ,δ -unsaturated ester **9** as the only product in excellent yield (85%). Furthermore, the reaction took place in a completely stereoselective way, as is expected for such suprafacial allylic rearrangements. The reduction of **9** with lithium borohydride (LiBH_4) furnished alcohol **10** (90% yield), and that, in turn, was treated with methanesulfonyl chloride in the presence of triethylamine to give methanesulfonate **11** in quantitative yield (96%). Compound **11** was converted into **5** by treatment with sodium azide (95% yield). With azidoalkene **5** in hand, we focused our attention on its conversion to the key intermediate **6**. Under thermal conditions, azides react with olefins through a 1,3-dipolar cycloaddition to form 1,2,3- Δ^2 -triazolines^[7] that – unlike their aromatic analogues (1,2,3-triazoles) – are generally not isolable and evolve after nitrogen loss to the corresponding imines.^[8] In particular, the intramolecular azide–olefin cycloaddition reaction (IAOC) has found broad application in the syntheses of complex molecules.^[8,9] Upon heating of azidoalkene **5** at 140 °C in toluene (sealed tube), a readily separable mixture of imine **6** (68% yield) and aziridine **13** (16% yield) was obtained. As anticipated, because of the configurationally labile nature of the enaminic C-3a position of **6**, a total epimerization took place at this center (see below). On the other hand, such an epimerization was not observed in aziridine **13**, because equilibration was not possible in this case. The use of other solvents such as DMF (*N,N*-dimethylformamide) and methanol or the employment of microwave heating resulted in lower yields and more complex mixtures of products. Furthermore, all attempts to decrease the amount of aziridine **13** by modifying the temperature and reaction times were unsuccessful, leading to similar ratios but lower yields.

As shown in Scheme 3, the reduction of imine **6** with sodium borohydride (NaBH_4) in the presence of methanol and the in situ protection of the generated amine with di-

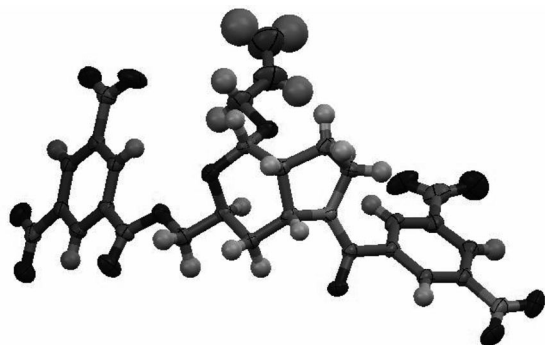


Scheme 2. Synthesis of key imine **6**.

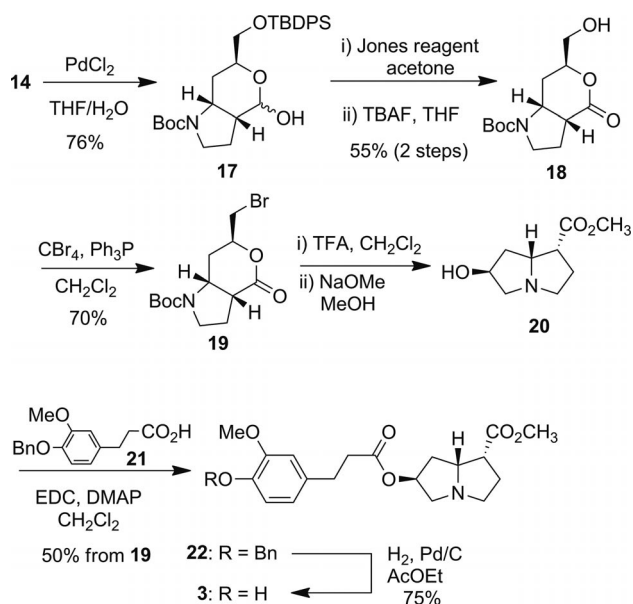
tert-butyl dicarbonate afforded intermediate **14** as a single diastereomer. As expected, the reduction of the imine functionality proceeded from the less hindered convex face of bicycle **6**. The relative *syn* stereochemistry between 3a-H, 7a-H, and 4-H was established with the aid of NOE experiments. These assignments were ultimately confirmed by the conversion of imine **6** into compound **16** through deprotection with TBAF (tetra-*n*-butylammonium fluoride), reduction of the resulting imino alcohol **15** with NaBH_4 , and a subsequent reaction with 3,5-dinitrobenzoyl chloride (3,5-DNBC) in the presence of Et_3N . The structure and relative stereochemistry of amide **16** was determined by single-crystal X-ray diffraction analysis (Figure 2).^[10]



Scheme 3. Synthesis of Boc-protected amine **14** and amide **16**.

Figure 2. X-ray structure of amide **16**.

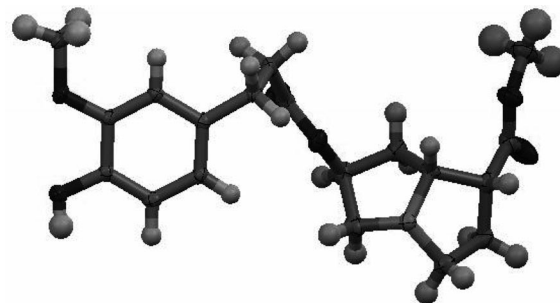
With the three stereocenters required for the synthesis of the amphorogynine C skeleton already installed, we turned our attention to the formation of the pyrrolizidine core. Treatment of compound **14** with palladium chloride^[11] in a mixture of THF/H₂O (9:1) afforded lactol **17** in moderate yield (Scheme 4). The oxidation of **17** to the corresponding bicyclic lactone **18** proved to be one of the most problematic steps in the synthesis. Although PCC (pyridinium chlorochromate), Dess–Martin periodinane, MnO₂, and TPAP (tetra-*n*-propylammonium perruthenate) were unsuccessful in promoting the oxidation,^[12] resulting in the recovery of unaltered starting material, exposing **17** to Jones reagent^[13] and subsequent treatment of the crude material with TBAF (see Exp. Sect.) provided **18** in a 55% combined yield. The treatment of the alcohol **18** with carbon tetrabromide in the presence of triphenylphosphane delivered the corresponding bromide **19** (70% yield). After some experimentation, we found that exposing compound **19** to trifluoroacetic acid and subsequent treatment with freshly prepared sodium methoxide afforded hydroxypyrrolizidine **20**, which was immediately esterified with the *O*-benzylated derivative of the hydroferulic acid **21**^[14] to afford **22** as single diastereoisomer



Scheme 4. Completion of total synthesis.

mer with an overall yield of 50% (3 steps). Finally, the elimination of the benzyl group by catalytic hydrogenation (H₂, Pd/C) cleanly afforded amphorogynine C (**3**) in 75% yield. The physical and spectroscopic data (¹H and ¹³C NMR) obtained for the synthetic material are in agreement with those previously reported in the literature.^[2,15]

Finally, slow concentration of a methanol solution of **3** afforded crystals suitable for X-ray diffraction analysis (Figure 3).^[10] Because the synthetic route from tri-*O*-acetyl-D-glucal is unambiguous with total stereocontrol, it confirms the structure of amphorogynine C proposed by Pais and co-workers^[2].

Figure 3. X-ray structure of amphorogynine C (**3**).

Conclusions

The first total synthesis of natural amphorogynine C was achieved. The key steps include an intramolecular 1,3-dipolar cycloaddition of an azide onto an alkene and subsequent reduction of the resulting imine to the corresponding amine. Finally, the proposed structure of amphorogynine C was confirmed by single-crystal X-ray diffraction analysis.

Experimental Section

General Methods: When it was appropriate, the reactions were carried out under argon, by using dry solvents and anhydrous conditions, unless it was stated otherwise. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Dry dichloromethane (DCM), tetrahydrofuran (THF), DMF, toluene, and diethyl ether were obtained by passing the previously degassed solvents through activated alumina columns. The reagents purchased were of the highest commercial quality and used without further purification, unless otherwise stated. Flash column chromatography was performed by using silica gel (60 Å pore size, 40–63 µm, Merck) or deactivated alumina (Brockmann I, Sigma-Aldrich). The reactions were monitored by thin layer chromatography (TLC) on silica gel-coated plates (Merck 60 F254). Detection was performed by using UV light and by charring the plate at ca. 150 °C, after dipping it into an aqueous solution of potassium permanganate (KMnO₄), an ethanolic solution of phosphomolybdic acid (PMA), or an ethanolic solution of ninhydrin. The yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous material, unless otherwise stated. The NMR spectroscopic data were recorded with Varian Unity-500, Inova-400, Mercury-400, and Inova-300 instruments and are calibrated by using the residual undeuterated solvent as an internal reference. The abbrevi-

ations used to explain multiplicities are s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad. High-resolution mass spectra (HRMS) were recorded with an Agilent 6520-Accurate-Mass LC/MS Q-TOF mass spectrometer. IR experiments were recorded with a Perkin–Elmer Spectrum One FTIR spectrometer. Optical rotations were performed with a Perkin–Elmer 241 MC polarimeter.

Ester 9: A mixture of alcohol **8** (5.0 g, 11.8 mmol) and trimethyl orthoacetate (22.1 mL, 118 mmol) was heated to 100 °C, and then propionic acid (0.09 mL, 1.18 mmol) was added. The mixture was stirred at 140 °C for 72 h. (The MeOH formed during the reaction was eliminated periodically with a rotary evaporator.) The solvent was evaporated, and the residual product was purified by flash chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 9:1). Ester **9** (4.82 g, 85%) was obtained as a colorless viscous oil. $[α]_D^{25} = +29.5$ ($c = 1.10$, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 7.68 (m, 4 H), 7.41 (m, 6 H), 5.93 (dddd, $J = 17.2$, 10.4, 6.2, 5.2 Hz, 1 H), 5.79 (m, 2 H), 5.29 (ddd, $J = 17.2$, 1.7, 1.6 Hz, 1 H), 5.18 (ddd, $J = 10.4$, 1.7, 1.3 Hz, 1 H), 4.80 (s, 1 H), 4.26–4.20 (m, 2 H), 4.06 (ddd, $J = 13.0$, 6.2, 1.3 Hz, 1 H), 3.73 (m, 2 H), 3.67 (s, 3 H), 2.60 (m, 1 H), 2.48 (dd, $J = 16.1$, 8.1 Hz, 1 H), 2.36 (dd, $J = 16.1$, 6.6 Hz, 1 H), 1.07 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 172.5, 135.8, 134.4, 133.6, 129.8, 127.8, 127.0, 126.0, 117.4, 98.2, 69.5, 68.6, 66.3, 51.8, 37.8, 35.8, 27.0, 19.4 ppm. FTIR (neat): $\tilde{\nu} = 3072$, 3048, 2931, 2858, 1739, 1647, 1590, 1473, 1428, 1391, 1361, 1267, 1113, 1027, 933, 823, 794, 740, 702 cm⁻¹. HRMS (ESI): calcd. for C₂₈H₄₀NO₅Si [M + NH₄]⁺ 498.2670; found 498.2668.

Alcohol 10: Lithium borohydride (272 mg, 12.5 mmol) was added to a solution of compound **9** (2.0 g, 4.16 mmol) in anhydrous THF (10 mL) at 0 °C. Then, MeOH (1 mL) was added dropwise. The mixture was stirred at 0 °C for 30 min and then at room temperature for another 4 h. The mixture was cooled again to 0 °C and the reaction quenched by the addition of H₂O. The MeOH was evaporated, and the residue was extracted with EtOAc (3 × 60 mL). The combined organic layers were dried with MgSO₄, filtered, and concentrated in vacuo. The crude residue was purified by chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 8:2) to provide compound **10** (1.69 g, 90%) as a colorless oil. $[α]_D^{25} = +51.0$ ($c = 1.00$, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 7.69 (m, 4 H), 7.40 (m, 6 H), 5.94 (dddd, $J = 17.2$, 10.4, 6.2, 5.2 Hz, 1 H), 5.85 (m, 1 H), 5.75 (m, 1 H), 5.28 (ddd, $J = 17.2$, 1.6, 1.5 Hz, 1 H), 5.19 (ddd, $J = 10.4$, 1.6, 0.9 Hz, 1 H), 4.88 (s, 1 H), 4.23 (m, 2 H), 4.05 (ddd, $J = 12.9$, 6.3, 1.1 Hz, 1 H), 3.80–3.59 (m, 4 H), 2.33 (m, 1 H), 2.19 (br. s, 1 H), 1.73 (m, 2 H), 1.07 (s, 9 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 135.8, 134.4, 133.6, 129.8, 127.8, 126.7, 126.0, 117.5, 99.5, 69.3, 68.5, 66.3, 59.9, 36.9, 35.9, 27.0, 19.4 ppm. FTIR (neat): $\tilde{\nu} = 3072$, 3048, 2931, 2859, 1473, 1428, 1187, 1113, 1031, 823, 740, 703 cm⁻¹. HRMS (ESI): calcd. for C₂₇H₃₆NaO₄Si [M + Na]⁺ 475.2275; found 475.2262.

Mesylate 11: Et₃N (0.74 mL, 5.30 mmol) was added to a solution of alcohol **10** (1.0 g, 2.21 mmol) in CH₂Cl₂ (30 mL) at 0 °C, followed by the dropwise addition of MsCl (0.22 mL, 2.88 mmol) dissolved in CH₂Cl₂ (5 mL). The mixture was stirred at 0 °C for 30 min and then at room temperature for 2 h. The solvent was removed by rotary evaporation, and the residue was purified by column chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 8:2) to afford compound **11** (1.124 g, 96%) as a colorless oil. $[α]_D^{25} = +47.4$ ($c = 1.00$, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 7.69 (m, 4 H), 7.41 (m, 6 H), 5.93 (dddd, $J = 17.2$, 10.3, 6.3, 5.2 Hz, 1 H), 5.82 (m, 2 H), 5.29 (ddd, $J = 17.2$, 1.7, 1.6 Hz, 1 H), 5.20 (ddd, $J = 10.3$, 1.7, 1.3 Hz, 1 H), 4.78 (s, 1 H), 4.26 (m, 4 H),

4.05 (ddd, $J = 12.9$, 6.3, 1.6 Hz, 1 H), 3.75 (m, 2 H), 2.97 (s, 3 H), 2.31 (m, 1 H), 1.96 (td, $J = 13.9$, 6.9 Hz, 1 H), 1.83 (td, $J = 13.9$, 6.3 Hz, 1 H), 1.07 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 135.7, 134.3, 133.6, 129.8, 127.8, 127.4, 125.6, 117.6, 98.6, 69.6, 68.5, 67.5, 66.2, 37.6, 35.7, 33.0, 27.0, 19.4 ppm. FTIR (neat): $\tilde{\nu} = 3072$, 3032, 2931, 2858, 1736, 1647, 1589, 1473, 1428, 1359, 1176, 1114, 1030, 958, 823, 796, 742, 704 cm⁻¹. HRMS (ESI): calcd. for C₂₈H₃₈NaO₆SSi [M + Na]⁺ 553.2051; found 553.2046.

Azide 5: Mesylate **11** (800 mg, 1.51 mmol) was dissolved in anhydrous *N,N*-dimethylformamide (10 mL). Sodium azide (980 mg, 15.1 mmol) was added, and the mixture was heated at 60 °C for 2 h. Then, the solvent was removed in vacuo. The residue was dissolved in water, and the resulting solution was extracted with EtOAc (3 × 40 mL). The combined organic phases were dried with MgSO₄, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 85:15) to yield **5** (691 mg, 96%) as a colorless oil. $[α]_D^{25} = +67.2$ ($c = 1.00$, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 7.68 (m, 4 H), 7.40 (m, 6 H), 5.92 (dddd, $J = 17.2$, 10.2, 6.3, 5.2 Hz, 1 H), 5.79 (m, 2 H), 5.28 (ddd, $J = 17.2$, 1.7, 1.6 Hz, 1 H), 5.19 (ddd, $J = 10.3$, 1.7, 1.3 Hz, 1 H), 4.75 (s, 1 H), 4.22 (m, 2 H), 4.05 (ddd, $J = 12.8$, 6.3, 1.3 Hz, 1 H), 3.73 (m, 2 H), 3.32 (m, 2 H), 2.23 (m, 1 H), 1.71 (m, 2 H), 1.07 (s, 9 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 135.8, 134.4, 133.7, 129.8, 127.8, 127.0, 125.9, 117.5, 98.8, 69.5, 68.5, 66.4, 49.0, 36.7, 32.6, 27.0, 19.4 ppm. FTIR (neat): $\tilde{\nu} = 3072$, 3048, 2931, 2859, 2096, 1473, 1462, 1428, 1362, 1261, 1187, 1114, 1033, 823, 702 cm⁻¹. HRMS (ESI): calcd. for C₂₇H₃₅N₃NaO₃Si [M + Na]⁺ 500.2340; found 500.2316.

Imine 6: In a sealed tube, a solution of compound **5** (300 mg, 0.63 mmol) in toluene (10 mL) was heated at 140 °C for 24 h. The mixture was cooled to room temperature, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, gradient from CH₂Cl₂ to CH₂Cl₂/MeOH, 3%) to afford the desired imine **6** (192 mg, 68%) as a pale yellow, viscous oil and aziridine **13** (45 mg, 16%) as a dark yellow oil. Data for compound **6**: $[α]_D^{25} = +110.5$ ($c = 0.88$, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ = 7.69 (m, 4 H), 7.39 (m, 6 H), 5.86 (dddd, $J = 17.2$, 10.7, 5.9, 4.9 Hz, 1 H), 5.23 (ddd, $J = 17.2$, 1.7, 1.6 Hz, 1 H), 5.14 (ddd, $J = 10.7$, 1.7, 1.3 Hz, 1 H), 5.09 (d, $J = 4.7$ Hz, 1 H), 4.16 (ddd, $J = 13.3$, 4.9, 1.6 Hz, 1 H), 3.94 (m, 3 H), 3.79 (dd, $J = 10.7$, 5.6 Hz, 1 H), 3.72 (m, 2 H), 2.93 (m, 1 H), 2.65 (dd, $J = 14.0$, 2.9 Hz, 1 H), 2.30 (m, 1 H), 1.90 (m, 2 H), 1.06 (s, 9 H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 172.8, 135.7, 134.1, 133.5, 129.8, 127.8, 116.9, 98.5, 69.2, 67.7, 66.7, 60.2, 51.6, 34.4, 26.9, 22.8, 19.4 ppm. FTIR (neat): $\tilde{\nu} = 3071$, 3049, 2956, 2930, 2859, 1663, 1472, 1462, 1428, 1362, 1287, 1136, 1113, 1031, 823, 703 cm⁻¹. HRMS (ESI): calcd. for C₂₇H₃₆NO₃Si [M + H]⁺ 450.2459; found 450.2474. Data for aziridine **13**: $[α]_D^{25} = +29.9$ ($c = 0.97$, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 7.72 (m, 4 H), 7.40 (m, 6 H), 5.93 (dddd, $J = 17.2$, 10.3, 6.2, 5.2 Hz, 1 H), 5.29 (dd, $J = 17.2$, 1.6 Hz, 1 H), 5.20 (dd, $J = 10.3$, 1.6 Hz, 1 H), 4.60 (s, 1 H), 4.34 (td, $J = 6.2$, 2.3 Hz, 1 H), 4.15 (ddt, $J = 12.9$, 5.2, 1.5 Hz, 1 H), 4.01–3.87 (m, 3 H), 3.05 (m, 1 H), 2.81 (m, 2 H), 2.41 (m, 2 H), 2.16 (m, 1 H), 1.81 (m, 1 H), 1.08 (s, 9 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 135.8, 134.3, 133.5, 129.8, 127.8, 117.6, 98.0, 67.9 (2 C), 64.9, 49.0, 40.2, 38.4, 37.1, 36.6, 26.9, 19.3 ppm. FTIR (neat): $\tilde{\nu} = 3071$, 3049, 2956, 2931, 2858, 1472, 1463, 1428, 1391, 1362, 1190, 1113, 1089, 1029, 999, 823, 740, 703 cm⁻¹. HRMS (ESI): calcd. for C₂₇H₃₆NO₃Si [M + H]⁺ 450.2459; found 450.2478.

Boc-Protected Amine 14: To a solution of **6** (500 mg, 1.11 mmol) in MeOH (25 mL) at 0 °C was added NaBH₄ (84 mg, 2.22 mmol).

After 30 min, the mixture was warmed to room temperature and stirred for an additional 1 h. Then, a saturated solution of NH_4Cl (10 mL) was added, and the MeOH was removed under reduced pressure. The resulting residue was diluted with aqueous NaOH (1 N solution, 10 mL), and the mixture was thoroughly extracted with CH_2Cl_2 (3×40 mL). The combined organic phases were dried with MgSO_4 , filtered, and concentrated in vacuo. The crude amine was dissolved in CH_2Cl_2 (25 mL), and the resulting solution was cooled to 0°C . Et_3N (0.23 mL, 1.66 mmol) and (Boc) $_2\text{O}$ (291 mg, 1.33 mmol) dissolved in CH_2Cl_2 (3 mL) were sequentially added. The mixture was left at 0°C for 30 min and then at room temperature for 12 h. The solvent was removed under reduced pressure, and the crude oil was purified by column chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 9:1) to yield **14** (521 mg, 85%) as a colorless oil. $[\alpha]_D^{25} = -3.9$ ($c = 0.93$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): $\delta = 7.69$ (m, 4 H), 7.38 (m, 6 H), 5.89 (dddd, $J = 17.2, 10.5, 5.3, 4.9$ Hz, 1 H), 5.25 (d, $J = 17.2$ Hz, 1 H), 5.14 (ddd, $J = 10.5, 1.6, 1.4$ Hz, 1 H), 4.95 (d, $J = 4.9$ Hz, 1 H), 4.27 (m, 1 H), 3.96 (m, 3 H), 3.66 (m, 2 H), 3.52 (m, 1 H), 3.42 (m, 1 H), 2.48 (m, 1 H), 2.30 (m, 1 H), 2.12 (m, 1 H), 1.95 (m, 1 H), 1.79 (m, 1 H), 1.46 (s, 9 H), 1.05 (s, 9 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 155.1, 135.8, 134.8, 133.7, 129.8, 127.8, 116.4, 97.0, 68.5, 67.6, 66.8, 53.4, 47.5, 41.0, 28.0$ (2 C), 27.4, 27.1, 24.5, 19.4 ppm. FTIR (neat): $\tilde{\nu} = 3072, 3050, 2931, 2859, 1811, 1757, 1694, 1474, 1456, 1428, 1393, 1366, 1262, 1211, 1172, 1113, 1034, 824, 741, 703, 613$ cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{32}\text{H}_{45}\text{NNaO}_5\text{Si}$ $[\text{M} + \text{Na}]^+ 574.2959$; found 574.2975.

Imino Alcohol 15: Tetrabutylammonium fluoride trihydrate (320 mg, 1.02 mmol) was added to a solution of **6** (230 mg, 0.051 mmol) in THF (10 mL). The mixture was stirred at room temperature for 2 h. The solvent was evaporated, and the residual oil was purified by flash chromatography (silica gel, gradient from DCM to DCM/MeOH, 4%) to afford compound **15** (87 mg, 81%) as a yellow oil. $[\alpha]_D^{25} = +229.3$ ($c = 1.60$, CH_2Cl_2). ^1H NMR (300 MHz, CDCl_3): $\delta = 5.84$ (dddd, $J = 17.2, 10.6, 5.9, 5.1$ Hz, 1 H), 5.22 (ddd, $J = 17.2, 1.7, 1.6$ Hz, 1 H), 5.13 (ddd, $J = 10.4, 1.6, 1.5$ Hz, 1 H), 5.08 (d, $J = 4.6$ Hz, 1 H), 4.14 (ddt, $J = 13.3, 5.1, 1.5$ Hz, 1 H), 3.97–3.84 (m, 3 H), 3.75–3.58 (m, 3 H), 2.91 (m, 1 H), 2.38 (dd, $J = 13.9, 3.1$ Hz, 1 H), 1.88 (m, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 172.9, 133.9, 117.1, 98.8, 69.1, 67.9, 65.1, 60.1, 51.6, 33.5, 22.8$ ppm. FTIR (neat): $\tilde{\nu} = 3233, 2914, 2871, 1664, 1461, 1424, 1370, 1344, 1314, 1288, 1132, 1032, 979, 955, 820, 731$ cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{11}\text{H}_{18}\text{NO}_3$ $[\text{M} + \text{H}]^+ 212.1281$; found 212.1291.

Amide 16: Sodium borohydride (31 mg, 0.81 mmol) was added to a solution of compound **15** (86 mg, 0.41 mmol) in absolute methanol (5 mL) at 0°C . After 45 min, the reaction was quenched with a saturated NH_4Cl solution, and the resulting mixture was concentrated under reduced pressure. The residue was diluted with aqueous NaOH (1 N solution, 5 mL), and the resulting solution was thoroughly extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried with MgSO_4 , filtered, and concentrated in vacuo. The crude material was dissolved in CH_2Cl_2 (10 mL), and the solution was cooled to 0°C . Et_3N (0.23 mL, 1.63 mmol) and 3,5-dinitrobenzoyl chloride (281 mg, 1.22 mmol) were sequentially added. After stirring at room temperature for 8 h, the reaction mixture was quenched with a saturated NH_4Cl solution, and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine (10 mL), dried with MgSO_4 , filtered, and concentrated in vacuo. The crude solid was purified by chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 6:4) to afford compound **16** (48 mg, 19%) as a yellow solid; m.p. $193\text{--}195^\circ\text{C}$. $[\alpha]_D^{25} = +0.09$ ($c = 1.40$, CHCl_3). ^1H NMR

(400 MHz, CDCl_3): $\delta = 9.25$ (t, $J = 2.1$ Hz, 1 H), 9.19 (d, $J = 2.1$ Hz, 2 H), 9.12 (t, $J = 2.1$ Hz, 1 H), 8.76 (d, $J = 2.1$ Hz, 2 H), 6.01 (dddd, $J = 17.1, 10.6, 5.6, 4.9$ Hz, 1 H), 5.36 (ddd, $J = 17.1, 1.7, 1.6$ Hz, 1 H), 5.32 (dd, $J = 10.6, 1.5$ Hz, 1 H), 5.04 (d, $J = 5.4$ Hz, 1 H), 4.50 (d, $J = 5.6$ Hz, 2 H), 4.38 (m, 3 H), 4.07 (m, 2 H), 3.32 (t, $J = 9.0$ Hz, 1 H), 2.73 (m, 2 H), 2.04 (m, 1 H), 1.96 (m, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 166.9, 162.4, 148.8, 148.6, 140.3$ (2 C), 133.7, 129.6, 128.1, 122.7, 120.4, 117.7, 97.4, 68.7, 68.6, 62.1, 54.8, 52.3, 39.3, 27.0, 26.5 ppm. FTIR (KBr): $\tilde{\nu} = 3100, 2922, 1733, 1631, 1543, 1463, 1404, 1345, 1281, 1171, 1079, 1024, 921, 730, 721$ cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{25}\text{H}_{24}\text{N}_5\text{O}_{13}$ $[\text{M} + \text{H}]^+ 602.1365$; found 602.1365.

Lactol 17: Compound **14** (500 mg, 0.91 mmol) was dissolved in THF/ H_2O (9:1, 30 mL) at room temperature. Then, PdCl_2 (160 mg, 0.91 mmol) was added. After 8 h, additional catalyst (0.2 equiv.) was added, and, after 24 h, more catalyst (0.2 equiv.) was added. After 36 h, the reaction mixture was filtered through a plug of Celite. The filtrate was diluted with water, and the resulting mixture was extracted with Et_2O (3×50 mL). The combined organic layers were dried with MgSO_4 , filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 3:7) to afford the lactol **17** (354 mg, 76%) as a mixture of diastereomers (85:15). Data for major diastereomer: $[\alpha]_D^{25} = -2.1$ ($c = 0.62$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): $\delta = 7.67$ (m, 4 H), 7.39 (m, 6 H), 4.94 (d, $J = 5.0$ Hz, 1 H), 4.22 (m, 1 H), 4.08 (d, $J = 17.4$ Hz, 1 H), 3.97 (m, 1 H), 3.91 (m, 1 H), 3.54 (m, 2 H), 2.51 (m, 1 H), 2.33 (m, 1 H), 2.09 (m, 1 H), 2.06 (m, 1 H), 1.84 (m, 1 H), 1.45 (s, 9 H), 1.05 (s, 9 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 155.1, 135.8, 133.7, 129.9, 127.9, 98.0, 72.7, 68.1, 53.2, 47.4, 40.9, 28.8, 27.1$ (2 C), 26.6, 24.9, 19.4 ppm. FTIR (neat): $\tilde{\nu} = 3072, 3050, 1733, 1694, 1474, 1455, 1428, 1393, 1366, 1334, 1254, 1172, 1148, 1113, 1064, 824, 741, 704$ cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{29}\text{H}_{40}\text{NO}_5\text{Si}$ $[\text{M} - \text{H}]^- 510.2681$; found 510.2669. Data for minor diastereomer: $[\alpha]_D^{25} = -62.0$ ($c = 0.95$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): $\delta = 7.67$ (m, 4 H), 7.39 (m, 6 H), 4.69 (br. s, 1 H), 4.06 (m, 1 H), 3.99 (m, 1 H), 3.72–3.61 (m, 3 H), 3.59 (m, 1 H), 3.33 (ddd, $J = 10.6, 8.6, 8.4$ Hz, 1 H), 2.17 (m, 1 H), 1.84 (m, 2 H), 1.75 (m, 2 H), 1.46 (s, 9 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 155.3, 135.8, 133.5, 129.8, 127.8, 95.3, 71.2, 66.9, 54.5, 46.4, 43.9, 28.6, 28.7, 27.0, 26.4$ (2 C), 19.4 ppm. FTIR (neat): $\tilde{\nu} = 3072, 3050, 1733, 1694, 1474, 1455, 1428, 1393, 1366, 1334, 1254, 1172, 1148, 1113, 1064, 824, 741, 704$ cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{29}\text{H}_{42}\text{NO}_5\text{Si}$ $[\text{M} + \text{H}]^+ 512.2827$; found 512.2858.

Lactone 18: Lactol **17** (180 mg, 0.35 mmol) was dissolved in acetone (10 mL), and some anhydrous magnesium sulfate was added. Then, the solution was cooled to 0°C , and freshly prepared Jones reagent (2 mL) was added dropwise. After 30 min, the mixture was warmed to room temperature over 1 h. Isopropyl alcohol (5 mL) was then added to destroy the excess Jones reagent, and the mixture was filtered through a small pad of Celite. The solvent was removed in vacuo, and the crude residue was dissolved in a solution of NaHCO_3 , and the resulting mixture was extracted with EtOAc (3×40 mL). The combined organic layers were dried with MgSO_4 , filtered, and concentrated in vacuo. The crude oil was used in the next step without further purification. Tetrabutylammonium fluoride trihydrate (110 mg, 0.35 mmol) was added to a solution of the crude lactone in THF (15 mL). The mixture was stirred at room temperature for 2 h. The solvent was evaporated, and the residual product was purified by flash chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 2:8) to afford **18** (52 mg, 55%, 2 steps) as a colorless oil. $[\alpha]_D^{25} = -89.3$ ($c = 2.50$, CHCl_3). ^1H NMR (500 MHz, CDCl_3): $\delta = 4.47$ (m, 1 H), 4.21 (br. s, 1 H), 3.82 (d, J

= 11.3 Hz, 1 H), 3.68 (dd, J = 11.3, 4.9 Hz, 1 H), 3.52 (br. s, 1 H), 3.37 (dt, J = 11.1, 7.1 Hz, 1 H), 3.21 (m, 1 H), 2.33 (m, 1 H), 2.27 (m, 1 H), 2.19 (m, 1 H), 1.97 (ddd, J = 14.7, 10.5, 4.2 Hz, 1 H), 1.45 (s, 9 H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ = 172.5, 154.5, 77.0, 64.7, 53.6, 46.4, 43.2, 29.6, 28.6 (2 C), 28.1 ppm. FTIR (neat): $\tilde{\nu}$ = 3444, 2976, 2935, 2880, 1732, 1694, 1399, 1367, 1260, 1167, 1096, 1049, 856, 773 cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{13}\text{H}_{22}\text{NO}_5$ [$\text{M} + \text{H}$] $^+$ 272.1492; found 272.1495.

Bromide 19: Lactone **18** (100 mg, 0.37 mmol) was dissolved in CH_2Cl_2 (10 mL), and the solution was cooled to 0 °C. Carbon tetrabromide (184 mg, 0.56 mmol) and triphenylphosphane (147 mg, 0.56 mmol) were added, and the mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. Upon completion, the solvent was removed in vacuo, and the crude residue was purified by column chromatography (silica gel, gradient from hexanes to hexanes/EtOAc, 7:3) to obtain **19** (90 mg, 70%) as a white solid; m.p. 90–92 °C. $[\alpha]_D^{25}$ = –96.1 (c = 0.71, CHCl_3). ^1H NMR (500 MHz, CDCl_3): δ = 4.55 (m, 1 H), 4.19 (br. s, 1 H), 3.52 (m, 3 H), 3.36 (dt, J = 11.2, 7.3 Hz, 1 H), 3.23 (m, 1 H), 2.59 (m, 1 H), 2.24 (m, 2 H), 1.93 (ddd, J = 14.7, 10.6, 4.0 Hz, 1 H), 1.47 (s, 9 H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ = 171.5, 154.4, 74.8, 53.5, 46.4, 43.1, 33.4, 29.5, 28.6 (2 C), 28.0 ppm. FTIR (KBr): $\tilde{\nu}$ = 3449, 2960, 2926, 2854, 2097, 1739, 1694, 1394, 1367, 1260, 1168, 1115, 1042 cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{13}\text{H}_{24}\text{N}_2\text{O}_4\text{Br}$ [$\text{M} + \text{NH}_4$] $^+$ 351.0903; found 351.0927.

Compound 22: Bromide **19** (50 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (5 mL), and TFA (trifluoroacetic acid, 0.5 mL) was added dropwise. The reaction mixture was stirred for 90 min, and then the solvent was removed in vacuo. The crude amine was then dissolved in MeOH (5 mL), and freshly prepared NaOMe (solution in methanol, 1 mL) was added. The reaction was stirred at room temperature for 1 h, and the methanol was eliminated under reduced pressure. The crude residue was dissolved in HCl (5% solution), and the resulting mixture was extracted with diethyl ether (1 \times 10 mL). The aqueous layer was basified with NaOH (1 N solution), and the resulting solution was extracted with CH_2Cl_2 (3 \times 30 mL). The combined organic layers were dried with MgSO_4 , filtered, and concentrated in vacuo to obtain hydroxy ester **20** that was used without further purification. To a solution of the crude hydroxy ester in CH_2Cl_2 (4 mL), *O*-benzyl-protected hydroferulic acid **21** (43 mg, 0.15 mmol), DMAP [4-(dimethylamino)pyridine, 0.24 mg, 0.002 mmol], and 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide (40 mg, 0.21 mmol) were sequentially added. The reaction mixture was stirred at room temperature for 3 h and then filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, gradient from CH_2Cl_2 to $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 2%) to afford **22** (34 mg, 50%) as a white solid; m.p. 101–103 °C. $[\alpha]_D^{25}$ = –3.8 (c = 1.75, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ = 7.41 (m, 2 H), 7.33 (m, 2 H), 7.27 (m, 1 H), 6.77 (d, J = 8.0 Hz, 1 H), 6.73 (d, J = 2.0 Hz, 1 H), 6.64 (m, 1 H), 5.33 (t, J = 5.0 Hz, 1 H), 5.10 (s, 2 H), 4.14 (m, 1 H), 3.84 (s, 3 H), 3.68 (s, 3 H), 3.36 (d, J = 12.1 Hz, 1 H), 3.26–3.17 (m, 2 H), 2.88–2.78 (m, 4 H), 2.60 (td, J = 8.0, 2.7 Hz, 2 H), 2.14 (m, 1 H), 2.05 (m, 1 H), 1.95 (dd, J = 14.2, 7.0 Hz, 1 H), 1.72 (ddd, J = 14.2, 10.0, 5.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 173.0, 172.6, 149.7, 146.6, 137.4, 133.7, 128.6, 127.8, 127.3, 120.1, 114.2, 112.3, 75.8, 71.2, 64.3, 59.9, 56.0, 53.4, 52.0, 46.4, 36.1, 34.2, 30.5, 27.3 ppm. FTIR (KBr): $\tilde{\nu}$ = 3062, 3033, 2951, 2871, 1732, 1606, 1591, 1463, 1455, 1419, 1378, 1262, 1231, 1158, 1139, 1034, 853, 807, 736, 698 cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{26}\text{H}_{32}\text{NO}_6$ [$\text{M} + \text{H}$] $^+$ 454.2224; found 454.2240.

Amphorogynine C (3): Activated Pd/C (10%, 4 mg) was added in a single portion to a solution of **22** (35 mg, 0.077 mmol) in EtOAc

(3 mL). The mixture was stirred under H_2 for 2 h. Upon completion, the mixture was filtered through Celite by using several washes of EtOAc to ensure quantitative transfer. The solvent was removed under reduced pressure, and the crude residue was purified by column chromatography (silica gel, gradient from CH_2Cl_2 to $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 3%) to obtain amphorogynine **C** (**3**, 21 mg, 75%) as a white solid; m.p. 120 °C. $[\alpha]_D^{25}$ = –1.7 (c = 1.30, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ = 6.80 (d, J = 8.0 Hz, 1 H), 6.68 (d, J = 1.9 Hz, 1 H), 6.65 (dd, J = 8.0, 1.9 Hz, 1 H), 5.34 (t, J = 4.6 Hz, 1 H), 4.03 (m, 1 H), 3.85 (s, 3 H), 3.69 (s, 3 H), 3.28 (d, J = 11.8 Hz, 1 H), 3.19 (ddd, J = 8.2, 8.2, 8.2 Hz, 1 H), 3.13 (m, 1 H), 2.87 (m, 1 H), 2.85 (m, 2 H), 2.80 (m, 1 H), 2.58 (t, J = 8.5 Hz, 2 H), 2.12 (m, 1 H), 1.99 (m, 1 H), 1.90 (dd, J = 14.1, 6.9 Hz, 1 H), 1.68 (ddd, J = 14.1, 9.7, 5.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 173.5, 172.8, 146.7, 144.3, 132.3, 120.9, 114.6, 111.1, 76.3, 64.6, 60.4, 56.0, 53.8, 52.0, 46.7, 36.4, 34.4, 30.7, 27.3 ppm. FTIR (KBr): $\tilde{\nu}$ = 2952, 1732, 1597, 1516, 1452, 1436, 1377, 1275, 1236, 1202, 1156, 1125, 1035, 754 cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{19}\text{H}_{26}\text{NO}_6$ [$\text{M} + \text{H}$] $^+$ 364.1755; found 364.1765.

Supporting Information (see footnote on the first page of this article): Copies of all ^1H and ^{13}C NMR spectra.

Acknowledgments

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- [15] Because of the low absolute value of the optical rotation described for amphorogynine C, we measured it at different wavelengths: $[a]_D = -1.7$ ($c = 1.3$, CHCl_3), $[a]_{578} = -1.9$ ($c = 1.3$, CHCl_3), $[a]_{546} = -2.3$ ($c = 1.3$, CHCl_3), $[a]_{465} = -1.8$ ($c = 1.3$, CHCl_3), $[a]_{365} = -27.1$ ($c = 1.3$, CHCl_3). These values are in agreement with the negative sign for the optical rotation reported for the natural compound.^[2]

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Synthesis of Functionalized Bicyclic Imines *via* Intramolecular Azide-Alkene 1,3-Dipolar Cycloaddition/Intramolecular Stork Alkylation Cascade Reaction

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Abstract: A cascade intramolecular azide-alkene 1,3-dipolar cycloaddition/Stork alkylation reaction has been developed for the synthesis of functionalized cyclic imines with a pyrroline and piperidine structures, employing readily available ω -azido-dienes.

Keywords: azides; cycloaddition; piperidines; pyrrolines; Stork alkylation

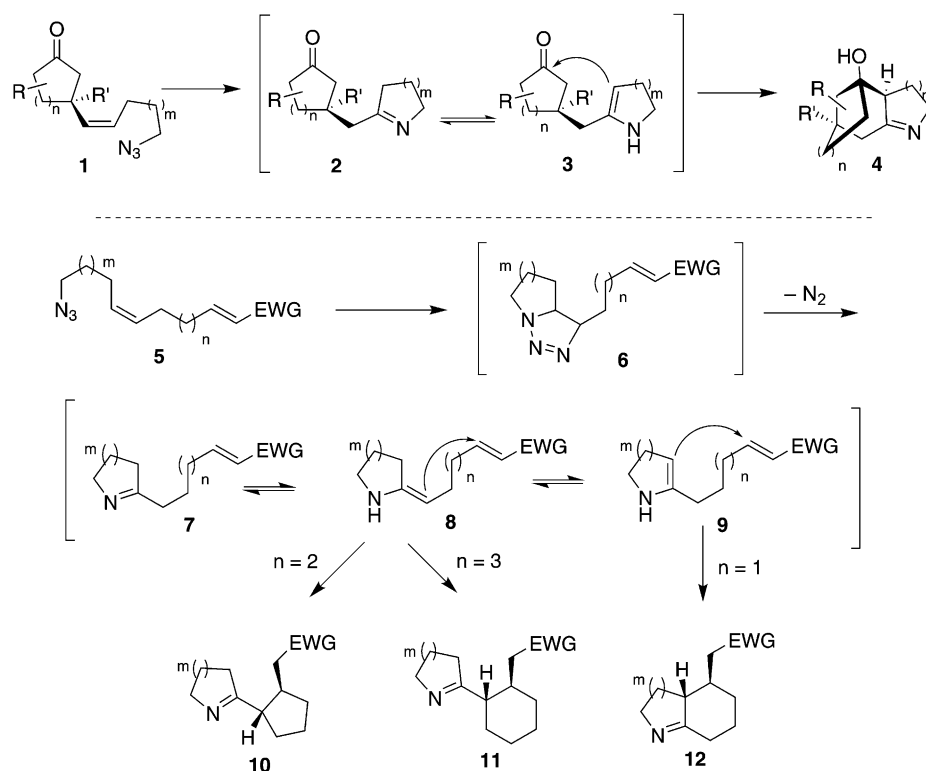
Five- and six- membered ring cyclic imines (1-pyrrolines and 1-piperidines, respectively) are common structural motifs in natural and synthetic compounds with diverse biological and pharmacological activities.^[1] During the last decades, different procedures for the preparation of cyclic imines have been developed.^[2] In addition, these heterocycles are interesting synthetic intermediates for the preparation of pyrrolizidine-, indolizidine- and piperidine-containing structures.^[3] Major advances have been made in the modification of cyclic imines, including the development of catalyst systems for asymmetric hydrogenation,^[4] transfer hydrogenation,^[4a,5] exploiting the electrophilic nature of the carbon-nitrogen double bond through Mannich-like reactions^[6] or through the irreversible addition of organometallic reagents.^[7] On the other hand, the modification of these heterocycles taking advantage of their ability to act as nucleophiles *via* imine-enamine tautomerism or through the preparation of the corresponding metalloenamines^[8] has been less exploited.

In connection with our interest in the development of new synthetic routes for the preparation of nitrogen-containing heterocycles,^[9] we have described an intramolecular azide-alkene 1,3-dipolar cycloaddition/enamine addition cascade reaction for the stereoselective preparation of polycyclic imino alcohols

(Scheme 1, *top*).^[10] We demonstrated that cyclic imines **2** obtained by an intramolecular azide-olefin cycloaddition reaction of readily available ω -azidoalkenes **1** can tautomerize to the corresponding enamines **3** and react with conveniently located carbonyl groups in a cascade process to afford polycyclic imino alcohols (**4**). Here we report a related new diastereoselective and efficient cascade reaction that provides rapid access to functionalized pyrroline- and piperidine-containing heterocycles.

Organic azides react in uncatalyzed thermal 1,3-dipolar cycloaddition reactions with olefins to form 1,2,3- Δ^2 -triazolines.^[11] Triazolines usually decompose after the loss of nitrogen to form aziridines and/or imines depending on the substituents and the reaction conditions.^[12] In recent years, this reaction and, in particular the *intramolecular azide-olefin cycloaddition* reaction (IAOC), has allowed many successful synthesis of complex molecules.^[13] We hypothesized that cyclic imines **7** obtained by the IAOC reaction of linear azidoalkenes **5** after decomposition of the resulting triazolines (**6**) (Scheme 1, *bottom*), could tautomerize to the corresponding exocyclic and endocyclic enamines **8** and **9** and react through an *intramolecular* Michael addition^[14] (Stork enamine alkylation)^[15] with conveniently located Michael acceptor groups to afford the functionalized bicyclic imines **10–12**. To the best of our knowledge, there are only two reports dealing with the Stork alkylation reaction of pyrroline- and piperidine-derived enamines with Michael acceptors^[16] and, in both cases, the conjugate additions were carried out in an *intermolecular way*.

Our working hypothesis was first evaluated with the readily available ω -azidodiene **13a**,^[17] which presents an α,β -unsaturated methyl ester as Michael acceptor. Several solvents and temperatures were screened and representative results are summarized in Table 1. In all cases we observed the formation of the desired bicyclic imine **14a** as only one diastereomer, except when water was used as solvent (entry 5),



Scheme 1. Proposed cascade reaction.

where no product of cyclization was detected. When we employed acetonitrile (entry 6) or THF (entry 7) as solvents, the yields were only moderate. On the other hand, better results were obtained with DMF (entries 1–3), toluene (entry 4) and MeOH (entry 8). We also carried out the reaction in DMF in a sealed tube (entry 3) but the yield was not improved and a longer reaction time was necessary to complete the reaction. Finally, the use of DMF as solvent, under microwave irradiation (140 °C, 2 h, entry 2) resulted

Table 1. Optimization of the reaction conditions for the synthesis of pyrroline **14a**.

Entry	Solvent	Temp. [°C]	Time [h]	Yield [%] ^[a]
1	DMF	MW, 120 °C	3	65
2	DMF	MW, 140 °C	2	78
3	DMF	oil bath, 120 °C	16	68
4	toluene	MW, 120 °C	4	70
5	H ₂ O	MW, 140 °C	2	0
6	CH ₃ CN	MW, 140 °C	3	56
7	THF	MW, 120 °C	4	59
8	MeOH	MW, 140 °C	2	67

^[a] Isolated yield after purification by flash chromatography.

as the most efficient conditions for this cascade process and the desired imine **14a** was isolated in 78% yield. Due to the configurational lability of the new stereogenic center contiguous to the imine functional group, there exists the possibility of equilibration *via* imine-enamine tautomerism. For this reason, the most stable *anti* relative configuration between the two substituents present in the cyclopentane ring was tentatively assigned.^[18]

In order to further explore the scope of this reaction we prepared substrates **13b–h** with different Michael acceptor groups in their structure. Gratifyingly, under the optimized reaction conditions (DMF, 140 °C, microwave heating) we obtained the corresponding pyrrolines **14b–h** with high yields and in a stereoselective way (Table 2). The cascade reaction was complete in only one or two hours with the α,β -unsaturated methyl ester (entry 1), nitrile (entries 2 and 3) and phenyl sulfone (entries 4 and 5) groups. We also carried out the reaction of substrates **13g** and **13h**, which contain a vinylphosphonate group as electrophile. Although the use of alkenylphosphonates as Michael acceptors is well documented,^[19] it has been practically limited to the employment of the more reactive bis-activated phosphonates containing electron-withdrawing groups (EWG) such as carbonyl, cyano or phosphoryl groups at the α position. As expected, the vinyl phosphonate group resulted to be less reactive and longer reaction times (8 h) were required to

Table 2. Synthesis of functionalized pyrrolines.^[a]

Entry	Substrate	Time [h]	Product	Yield [%] ^[b]
1		2		82
2		1		93
3		1		80
4		1		96
5 ^[c]		2		90
6		8		87
7		8		91

^[a] Reaction conditions: DMF, 140 °C, MW.

^[b] Isolated yield after purification by flash chromatography.

^[c] Toluene was employed as solvent.

obtain the desired imines **14g** and **14h** in excellent yields (entries 6 and 7). Finally, only complex mixtures of products were obtained when α,β -unsaturated ketones were used as Michael acceptor functionalities under the standard reaction conditions.

We also examined the synthesis of 1-piperideines employing this methodology. Different solvents were screened with the readily available ω -azidodiene **15a** (Table 3). When DMF was employed, piperideine **16a**

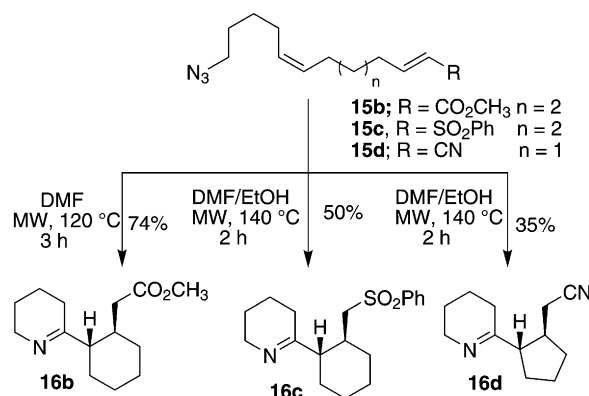
was obtained after 3 h, under microwave irradiation (140 °C), in a 59% yield (entry 1). Similar results were observed with toluene (entry 2) and MeOH (entry 4). Finally, employing a mixture of DMF/EtOH (4:1) at 140 °C (entry 3), we obtained **16a** in a similar yield (63%), but shorter reaction times (2 h) were required.

As shown in Scheme 2, we prepared the functionalized piperideines **16b–d** by applying similar reaction

Table 3. Optimization of the reaction conditions for the synthesis of piperideine derivatives.

Entry	Solvent	Temp. [°C]	Time [h]	Yield [%] ^[a]
1	DMF	MW, 140 °C	3	59
2	toluene	MW, 120 °C	4	52
3	DMF/EtOH	MW, 140 °C	2	63
4	MeOH	MW, 140 °C	3	60

^[a] Isolated yield after purification by flash chromatography.


Scheme 2. Synthesis of functionalized piperideines.

conditions to substrates **15b–d**. Nevertheless, the yields of these six-membered ring imines were not as high as those previously obtained for the analogous five-membered ring pyrrolines, probably because of their low stability and high propensity to undergo spontaneous oxidation during their purification.^[20] We also tried to prepare other related 1-piperideines but unfortunately they could not be isolated due to decomposition during the isolation and purification process.

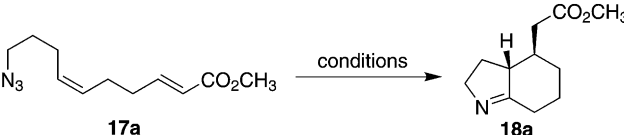
Finally, the reactivity of ω -azidodienes with the general structure **5** (Scheme 1), where the alkene functionalities are linked by only two methylene groups ($n=1$), was examined. In this case, tautomerization of the transient cyclic imines generated after the IAOC reaction to the endocyclic enamines **9** and subsequent 6-*exo*-trig cyclization *via* conjugate addi-

tion to afford the corresponding bicyclic imines with hexahydroindole core was expected. For this purpose we prepared compound **17a** and screened different reaction conditions in order to obtain the corresponding bicyclic imine **18a** (Table 4). When using DMF as solvent (entry 1) we obtained the desired product in 55% yield as only one diastereomer. We then tried to use toluene (entry 2) but after 4 h at 120 °C in the microwave reactor we only isolated the intermediate imine resulting from the 1,3 dipolar cycloaddition but not the product of the conjugate addition. When using a mixture of toluene and EtOH (4:1) (entry 3) the Michael addition took place but the product was obtained in low yield (30%). Finally we were pleased to find that the best result was obtained when MeOH was employed as solvent (entry 4), affording the desired hexahydroindole in a 68% yield.

Applying these conditions (MeOH, 140 °C, MW) we prepared bicyclic imines **18b–e**, starting from the corresponding linear azido alkenes **17b–e** (Table 5). Remarkably, the cascade reaction worked with substrates bearing α,β -unsaturated ketones groups as Michael acceptors (**17c–e**), affording the correspondent bicyclic imines **18c–e** in moderate yields in a stereoselective way. Of particular interest are compounds **18c** and **18e**: they possess both imine and α -methylene carbonyl groups in their structure, thus opening the possibility of carry out intramolecular Mannich-type reactions in order to access more complex structures.

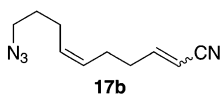
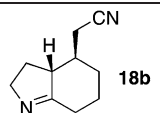
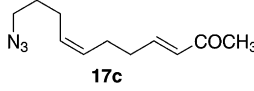
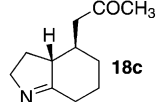
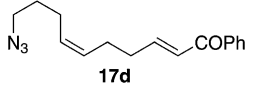
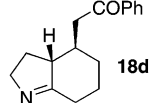
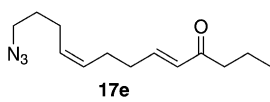
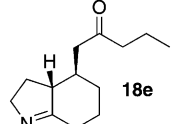
In summary, an efficient stereoselective intramolecular azide-olefin cycloaddition/Stork alkylation reaction cascade of ω -azidodienes for the preparation of diverse pyrroline- and piperideine-containing structures has been developed. Further developments of

Table 4. Optimization of the reaction conditions for the synthesis of hexahydroindole derivatives.

				
Entry	Solvent	Temp. [°C]	Time [h]	Yield [%] ^[a]
1	DMF	MW, 140 °C	2	55
2	toluene	MW, 120 °C	4	0
3	toluene/EtOH	MW, 120 °C	4	30
4	MeOH	MW, 140 °C	2	68
5	EtOH	MW, 140 °C	3	54

^[a] Isolated yield after purification by flash chromatography.

Table 5. Synthesis of functionalized hexahydroindole derivatives.^[a]

Entry	Substrate	Time [h]	Product	Yield [%] ^[b]
1		2		70
2		1		64
3		2		55
4		2		66

^[a] Reaction conditions: MeOH, 140 °C, MW.

^[b] Isolated yield after purification by flash chromatography.

this methodology, including mechanistic insight and enantioselective version as well as its application to the total synthesis of different alkaloids are currently in progress and will be reported in due course.

Experimental Section

Caution: All organic azides should be treated as potential explosion hazards.

Compound 14a {rac-Methyl 2-[(1R,2S)-2-(3,4-Dihydro-2H-pyrrol-5-yl)cyclopentyl]acetate}

A solution of compound **13a** (70 mg, 0.29 mmol) in dry DMF (13 mL) was heated in a microwave reactor at 140 °C for 2 h. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude reaction mixture was then purified by chromatography (silica gel, gradient from dichloromethane to 2% methanol in dichloromethane) to afford compound **14a** as a yellow oil; yield: 48 mg (78%). ¹H NMR (400 MHz, CDCl₃): δ = 3.75 (m, 2H), 3.61 (s, 3H), 2.47 (m, 4H), 2.39 (m, 1H), 2.23 (dd, *J* = 14.9, *J* = 8.3 Hz, 1H, CH₂CO₂CH₃), 2.02–1.86 (m, 2H), 1.83 (m, 2H), 1.66 (m, 3H), 1.29 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 180.1 (C=N), 173.6 (C=O), 60.6, 51.5, 49.8, 40.1, 39.1, 34.8, 32.4, 30.6, 24.2, 22.6; FT-IR (neat): ν_{max} = 2952, 2869, 1738, 1637, 1436, 1372, 1295, 1255, 1197, 1175, 1017, 986 cm⁻¹; HR-MS (ESI): *m/z* = 210.1499, calcd. for C₁₂H₂₀NO₂ [M+H]⁺: 210.1489.

Compound 16a {rac-Methyl 2-[(1R,2S)-2-(3,4,5,6-Tetrahydropyridin-2-yl)cyclopentyl]acetate}

A solution of compound **15a** (80 mg, 0.31 mmol) in a mixture of DMF/EtOH (12 mL, 4:1) was heated in a microwave reactor at 140 °C for 2 h. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The resulting reaction crude was then purified by chromatography (silica gel, gradient from dichloromethane to 3% methanol in dichloromethane) to afford compound **16a** as a pale yellow oil; yield: 44 mg (63%). ¹H NMR (300 MHz, CDCl₃): δ = 3.63 (s, 3H, CO₂CH₃), 3.56 (m, 2H), 2.52–2.36 (m, 3H), 2.35–2.25 (m, 2H), 2.19 (m, 1H), 2.01–1.88 (m, 2H), 1.74–1.55 (m, 7H), 1.30 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 173.8 (C=N), 169.1 (C=O), 55.6, 51.7 (CO₂CH₃), 48.1, 40.1, 38.9, 32.7, 30.9, 27.1, 24.3, 21.7, 19.3; HRMS (ESI): *m/z* = 224.1642, calcd. for C₁₃H₂₂NO₂ [M+H]⁺: 224.1645; FT-IR (neat) ν_{max} = 2952, 2869, 1738, 1637, 1436, 1372, 1295, 1255, 1197, 1175, 1017, 986, 881 cm⁻¹.

Compound 18a {rac-Methyl 2-[(3aR,4R)-3,3a,4,5,6,7-Hexahydro-2H-indol-4-yl]acetate}

A solution of compound **17a** (60 mg, 0.27 mmol) in dry MeOH (12 mL) was heated in a microwave reactor at 140 °C for 2 h. The mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The crude reaction mixture was then purified by chromatography (silica gel, gradient from dichloromethane to 3% methanol in dichloromethane) to afford compound **18a** as a yellow oil; yield: 36 mg (68%). ¹H NMR (400 MHz, CDCl₃): δ =

3.87 (m, 1H), 3.66 (s, 3H, CO₂CH₃), 3.58 (m, 1H), 2.66 (m, 1H), 2.42 (dd, *J* = 14.8, *J* = 4.6 Hz, 1H, CH₂CO₂CH₃), 2.32 (m, 1H), 2.21 (dd, *J* = 14.8, *J* = 8.8 Hz, 1H, CH₂CO₂CH₃), 2.15–2.08 (m, 2H), 1.95 (m, 1H), 1.87 (m, 1H), 1.68 (m, 1H), 1.49–1.40 (m, 2H), 1.25 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 178.3 (C=N), 173.1 (CO₂CH₃), 59.1, 53.3, 51.7 (CO₂CH₃), 42.7, 40.4 (CH₂CO₂CH₃), 31.4 (2C), 28.4, 25.2; HRMS (ESI): *m/z* = 196.1351, calcd. for C₁₁H₁₈NO₂ [M+H]⁺: 196.1293; FT-IR (neat) ν_{max} = 2949, 2866, 1737, 1652, 1568, 1436, 1234, 1195, 1155, 1099, 1012, 982 cm⁻¹.

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